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Trial designs to improve enrollment of older adults

Guiding principles:

- Trial objectives drive study design, selection of endpoints and intervention, and eligibility criteria
- Focus on designs that have the potential to improve accrual of older patients in NCI-sponsored trials

Objective:

- Safety or tolerability
- Efficacy
- Effectiveness
- Implementation

Endpoint:

- Safety: Adverse Events (CTCAE or PRO-CTCAE), dose modifications (reduction, delay, or discontinuation)
- Efficacy: Overall survival (OS), progression free survival (PFS), overall response rate (ORR), treatment failure-free survival (TFFS), time to treatment failure (TTF), Relapse-free survival (RFS)
- HRQoL: Function (Physical, Mental, Social, …), QOL
- GA outcomes

Trial Design and Examples	Objective	Endpoint	Eligibility	Intervention	Role of geriatric assessments (A, B, C, D, E)*	Comments/other recommendations
Older-patient specific (single arm, randomized, or pragmatic) – Examples: CALGB 49907, A171601, A171901, GOG-0273, FOCUS2, EA2186	Any listed above; examples include evaluate effectiveness of therapy adapted to older adults or intervention relevant to a subgroup of older patients, e.g. frail or vulnerable older patients; efficacy trials could be non-inferiority or superiority	Any listed above	Depending on trial objectives; Below are examples from completed NCI-sponsored trials. **GOG-0273:** previously untreated (except surgery); age 70+, but later restricted to 75+; PS 0-3 **CALGB 49907:** no prior chemo; age 65+; PS 0-2; **A171601:** no prior CDK inhibition, age 70+; PS was unrestricted, but changed to 0-2 **A171901:** first-line (in metastatic setting); age 70+; don't see a PS restriction **FOCUS2:** Previously untreated (in advanced setting?); unfit for full-dose chemo; Older adults *or* frail; PS 0-2	Approved agents, adapted therapy for specific patient population, GA-based intervention… Below are examples from completed trials. **GOG-0273:** carboplatin +/- paclitaxel (patient and physician chose; could be adjuvant or neoadjuvant) **CALGB 49907:** SOC chemo (CMF or doxorubicin + cyclophosphamide; pt/physician choice) vs. capecitabine **A171601:** palbocyclib letrozole or fulvestrant (physician choice) **A171901:** pembrolizumab +/- carboplatin and	Describe patient population (A), define eligibility (B), GA measures as outcomes (C), evaluate GA-based intervention (D), predict toxicity (E)	- Good design for evaluating efficacy of less toxic treatment for older, frail, or vulnerable patients - Good design for evaluating safety or tolerability of approved agents in older, frail, or vulnerable patients - Good design for evaluating GA-based intervention

				pemetrexed (patient/physician choice?) **FOCUS2:** Leucovorin + fluorouracil +/- oxaliplatin vs. capecitabine +/- oxaliplatin (2x2 factorial design)		
Parallel cohort (separate from main trial cohort, single arm or randomized) EXAMPLES: --leukemia trial (A041703): which includes two cohorts of the same sample sizes so 50% in OA (untreated) and 50% younger (and may have received HCT)	To evaluate new treatment in OA (can be designed to test OA-specific hypotheses)	Any listed above (combination of endpoints aligned with younger cohort and some OA-specific endpoints)	Parallel study is enrolling general population or fit older adults (thought that much older or less fit patients would not enroll at prevalence that in older adults)	-Same therapeutic intervention with OA specific endpoints and safety considerations (e.g., upfront dose reduction) or an adapted therapy option	Define eligibility for OA cohort (B), GA measures as outcomes (C), predict toxicity (E),	Preferred over extended cohort, appropriate design to evaluate treatment in OA concurrently with a cohort of younger patients; sample size determined separately by cohort; allows enrollment to be closed by cohort and results published separately; should provide a compelling case for why OA need a separate cohort.
Stratified/blocked randomized design (stratification can occur not only based on age, but on factors more prevalent in older patients, like comorbidity or	Efficacy; Evaluate outcomes in older subgroup (typically not powered for OA-specific hypotheses)	Efficacy, safety, or QOL defined by overall trial	Same as overall trial eligibility		Define eligibility and/or stratification (B)	Sample size for OAs is part of trial total sample size, typically not powered to test treatment effect in OAs; due to limited sample size and limited ability to access OA-specific outcomes, OA accrual is unlikely to improve with this design.

ADL/IADL dependence.						
Embedded study (cohort) – A041202	In addition to safety and efficacy, evaluate association between treatment functioning in OA consented to embedded study	Efficacy, safety, QOL, functioning	Same as overall trial eligibility		Define eligibility (B), predict toxicity (E)	Typically an optional component of a large trial where patients choose whether or not to participate; potential selection bias from patient's choice whether to participate. Additionally, the potential limited sample size may prevent evaluation of OA-specific outcomes. Similar to Design 3, OA accrual is unlikely to improve with this design. Good setting for correlative biology studies. Or cancer/treatment-related aging studies
Pragmatic trial – Examples: A171601 and A1719101	Effectiveness, safety or tolerability; Evaluate effectiveness of approved agents/therapy in OAs	Effectiveness, safety or tolerability QOL, functioning—as much as possible use data collected in real world (e.g., from EMR)	Patient population as broad as possible, fit to frail and study how treatment is or is not implemented based on real world setting	-model of care intervention vs flexibility of choices based on GA, patient preferences, or other factors -Usual care likely the comparator	GA can be used for eligibility (or specific measures can be used; B), outcomes (C), predict toxicity (E), as part of intervention (D)	PRECIS (scale for pragmatic studies) Inform how safe and effective approved agents/therapy for OAs, relax eligibility, follow-up requirements
Post-marketing surveillance	Evaluate safety in OA for approved agents/therapy					Not in NCI purvue

* A, B, C, D, E correspond to rows in the GA measure table.

Geriatric Assessment

A. Use of geriatric assessment in clinical trials-what are the research gaps?

- Utilize GA to characterize patient heterogeneity (i.e. baseline description)
- Utilize GA to guide treatment allocation
  - GA as eligibility (i.e. fit, vulnerable GIANT trial)
  - GA as the intervention to guide treatment intensity (i.e. lung cancer trial)
- Utilize GA to directed supportive care –symptoms/function
- Utilize GA to guide care delivery interventions—prevent hospitalization etc
- Utilize GA to evaluate survivorship—i.e. GA as outcome to understand impact on functional domains.

B. Fitness evaluation for treatment assignment*

1. Validated tools and need for new instruments (fit for purpose)
   i. GA battery (i.e. CARG)
   ii. Limited set of GA measures (i.e. MM frailty= ADL/IADL, CCI)
   iii. GA screening tool (i.e. G8)
   iv. Single item measures (i.e. gait speed)

   *Would benefit from core set of measures that are refined for specific settings

2. Treatment dependent?
   i. Choice of measures and predictive utility may be tx dependent if selected items used in particular—i.e. more or less sensitive to change, prevalence estimates may differ, resilience requirements may differ depending on intensity of tx
3. Cancer type dependent?
   i. Same as above, depends on use—predict outcomes then yes

Key Principles:

1. GA measures should be “fit for purpose”—matching measure selection to the study goals, setting, existing evidence
2. Use of existing validated measures/tools are favored when suited to achieve #1
3. Clinical decision phase (should a patient go on trial designed for all adults; use guidelines) vs specific geriatric oncology trials for more vulnerable patients
4. Each of the Table rows are not mutually exclusive—however, primary reason for including GA should be clear because this guides selection of measures

Table: Considerations when selecting GA measures in trials design

Role of GA or GA Measures in Trial Design	**Rationale**	**Considerations**	**Examples**	**Strategies/Measures**
Evaluate and describe the patient population	-Understanding baseline heterogeneity can help with translation of results to patients in the clinic who will most likely benefit -Can use in adaptive trial design or preplanned subset analyses to evaluate who is more or less likely to benefit	How will the information be used in the context of the study analyses, interpretation? What is known in this disease or treatment setting to inform measure selection?	-Muss et al, CALGB trial of adjuvant chemotherapy NEJM, 2009 -Seymour et al, FOCUS-2 trial, Lancet Oncology, 2011 -Grunwald et al., sarcoma RCT, JCO, 2020	-Alliance GA battery -Selected GA measures depending on domain of interest for specific population
Define eligibility: Identify older patients who may be more vulnerable to adverse outcomes	GA-based measures can be included as eligibility to enroll vulnerable older adults onto trials (historically often done with age or PS) or to enroll "fit" patients etc.	Key point in selecting measures: what is the intended use of the eligibility measures? -to exclude "frail"? -to include "fit"? -to focus on neither fit nor frail (GIANT)?	-URCC 13059 which included patients with at least one GA domain impairment other than polypharmacy -GIANT trial—select vulnerable patients -IFM study: selecting nonfrail but transplant ineligible patients for triplet vs quadruplet -HOVON – selecting int-fit and frail patients for phase 2 attenuated treatment Merli et al. Anziter3 trial, Leukemia and Lymphoma, 2012 (select fit patients for randomization)	-Full GA to evaluate GA domains (one or more positive) -Limited set of GA measures known to predict adverse outcomes in specific populations (MM, lymphoma, Gyn onc) -Screening items (G8 or VES-13)

GA measures as <u>outcomes</u>: Include as a study aim to examine the effect of intervention on GA measures such as function to characterize "tolerability to tx" and understand aging related changes during survivorship.	Outcomes as captured by GA measures are important endpoints for older adults (e.g., function, cognition)	Should be sensitive to change over time Statistical plan pre-specifies approach (change score vs dichotomous decline outcome vs longitudinal modeling vs time to deterioration) Applicable to therapeutic and survivorship studies GA and global HRQOL are not interchangeable although care should be taken to minimize overlap in PRO items	-URCC 13059 (ASCO annual meeting 2020) -CALGB 361006 (AML) -JNCCN systematic review in press summarizes 44 example studies (Loh et al., Characteristics Associated with Functional Changes During Systemic Cancer Treatments: A Systematic Review Focused on Older Adults)	-Specific measures validated for that outcome (e.g, IADL for function, SPPB for physical performance), and data to support that measure can capture change over time or be valuable for group comparisons -Need to leverage data on function that is collected as part of a QOL instrument that is often not analyzed (EORTC QLQ-C30) -Need to understand decline in functional outcomes AND improvement/recovery/resilience
Evaluate a GA-based model as an <u>intervention</u>	Two main ways that the GA is integrated into the trial design as an intervention: 1. GA can guide the allocation of cancer treatment 2. GA can guide GA-directed management (supportive care, care delivery, etc)	What is known about the GA in the specific treatment setting to inform how GA influences treatment allocation? (e.g. use established toxicity prediction model [CARG or CARG-BC] to allocate patients into low, medium, high risk of toxicity groups and tailor treatment approach by risk group)	GA treatment allocation <u>intervention:</u> -Corre, et al; JCO, 2016 - ELAN-FIT and ELAN-UNFIT; Guigay et al. Annals of Oncology 2019 (ESMO abstract) - Antonio et al, British Journal of Cancer, 2018 -UK Myeloma XIV FITNESS trial: reactive vs proactive dose adjustment based on frailty	-GA domains -Tools that incorporate GA measures to risk stratify (e.g. CARG toxicity tool); -selection of tools as appropriate for patient population; -models for integrating GA-directed management into oncology care (multiple models published; see trial list for different examples of models)

		Consideration for how fit, vulnerable, frail defined; how impairments in different GA domains might not all be "equal" (e.g. positive depression screen flagging impaired psychological domain may not be appropriate for defining frailty)	https://clinicaltrials.gov/ct2/show/NCT03720041 GA supportive care intervention: -URCC 13070 and 13059; Mohile et al. JAMA Oncology, 2020 -URCC 13059; Mohile et al, ASCO 2020 annual meeting -Spina at al, lymphoma 2012 - Puts,e t al, Supportive Care in Cancer, 2017 - Magnuson, et al. Supportive Care in Cancer, 2017 - Kalsi, et al. British Journal of Cancer, 2015 -ELAN-ONCOVAL; Mertens, et al. ASCO 2019 annual meeting - Ommundsen et al; Colorectal Disease, 2017 (Surgical Oncology) Ongoing trials: -Brugel, et al. BMC Cancer (protocol paper) for EGeSOR. -URCC 19178	
Examine relationships between aging-related conditions and tolerability of	GA measures can help increase understanding of how baseline patient characteristics are associated with tolerability; this can help physicians and patients make treatment	Defining tolerability endpoints is important prior to choosing GA measures. HRQoL could be an endpoint in this type of study but is not the baseline tool.	Examples: Cytotoxic Therapy: 1) CARG chemotoxicity calculator studies (Hurria JCO 2016; Magnuson JCO 2020)	CARG chemotherapy toxicity calculator CRASH toxicity calculator PACE: Pre-operative assessment in elderly cancer patients).

therapeutic strategies -GA to predict toxicity	decisions and improve informed consent.	Choosing specific GA domains can be considered rather than the entire GA. Screening GAs also reasonable. Frailty assessments based on GA domains have also been used Serial GAs (at baseline and at follow-up intervals) can also be considered in these study designs as functional outcomes are key for assessing tolerability (see above GA as outcomes above)	2) CRASH toxicity studies: Extermann et al. Cancer 2012. Cancer or Drug Specific: Hurria; Clin Breast Cancer 2019. Surgery: 1) Audisio (PACE studies): Audisio et al. Crit Rev Oncol Hematol 2008. 2) MPI score: Pata et al. J. Surg Oncol. 2021. Radiotherapy: 1) VanderWalde et al. Int J Radiat Oncol Biol Phys 2017. 2) H&N data: Pottel 2 BMC Cancer 2015. Immunotherapy: 1) Gomes et al. ELDERS study ESMO Open 2021.	MPI: Multidimensional Prognostic Index GA measures (used as the predictive tool alone in some studies) (e.g., ADLs; ADLs) Abbreviated screening tools such as G8 or VES-13

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Adjuvant Chemotherapy in Older Women with Early-Stage Breast Cancer

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ABSTRACT

BACKGROUND

Older women with breast cancer are underrepresented in clinical trials, and data on the effects of adjuvant chemotherapy in such patients are scant. We tested for the noninferiority of capecitabine as compared with standard chemotherapy in women with breast cancer who were 65 years of age or older.

METHODS

We randomly assigned patients with stage I, II, IIIA, or IIIB breast cancer to standard chemotherapy (either cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide plus doxorubicin) or capecitabine. Endocrine therapy was recommended after chemotherapy in patients with hormone-receptor–positive tumors. A Bayesian statistical design was used with a range in sample size from 600 to 1800 patients. The primary end point was relapse-free survival.

RESULTS

When the 600th patient was enrolled, the probability that, with longer follow-up, capecitabine therapy was highly likely to be inferior to standard chemotherapy met a prescribed level, and enrollment was discontinued. After an additional year of follow-up, the hazard ratio for disease recurrence or death in the capecitabine group was 2.09 (95% confidence interval, 1.38 to 3.17; P<0.001). Patients who were randomly assigned to capecitabine were twice as likely to have a relapse and almost twice as likely to die as patients who were randomly assigned to standard chemotherapy (P=0.02). At 3 years, the rate of relapse-free survival was 68% in the capecitabine group versus 85% in the standard-chemotherapy group, and the overall survival rate was 86% versus 91%. Two patients in the capecitabine group died of treatment-related complications; as compared with patients receiving capecitabine, twice as many patients receiving standard chemotherapy had moderate-to-severe toxic effects (64% vs. 33%).

CONCLUSIONS

Standard adjuvant chemotherapy is superior to capecitabine in patients with early-stage breast cancer who are 65 years of age or older. (ClinicalTrials.gov number, NCT00024102.)

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Age is the major risk factor for breast cancer.[1] In the United States, the average age at the diagnosis of breast cancer is approximately 63 years, and most deaths from breast cancer occur in women 65 years of age or older. Breast cancer in older women is not always managed according to treatment guidelines,[2-4] and such lapses can adversely affect survival.[5,6] Although adjuvant chemotherapy has improved survival among women with early-stage breast cancer,[7,8] the Oxford Overview analysis of 15-year results included too few patients older than 70 years of age to assess the effect of chemotherapy in that age group accurately.[7] Older women with breast cancer who are in good health tolerate chemotherapy about as well as younger patients,[9,10] and the more severe toxicity of chemotherapy in older patients[11] has not meaningfully affected the benefits of adjuvant chemotherapy.[12]

We report here the results of the Cancer and Leukemia Group B (CALGB) 49907 trial, which was designed specifically to compare the efficacy of standard chemotherapy (either cyclophosphamide, methotrexate, and fluorouracil [CMF] or doxorubicin plus cyclophosphamide) with the oral fluorouracil prodrug, capecitabine, in women with early-stage breast cancer who were 65 years of age or older. Patients often prefer oral to intravenous chemotherapy,[13] and an effective oral agent for adjuvant treatment would be important for treating older women with breast cancer.

Capecitabine has substantial antitumor activity in metastatic breast cancer, with response rates of approximately 30%.[14,15] In small, randomized trials involving women with metastatic breast cancer, the activity of capecitabine was similar to that of paclitaxel[16] or CMF,[17] making it a potential alternative to standard adjuvant chemotherapy.

METHODS

PATIENTS

Eligible women were 65 years of age or older and had operable, histologically confirmed adenocarcinoma of the breast, with a performance status of 0 to 2 (according to the National Cancer Institute [NCI] criteria) and a tumor diameter that was more than 1 cm; status with respect to estrogen receptor, progesterone receptor, and human epidermal growth factor receptor type 2 (HER2) was not specified as an eligibility criterion. Adequate hematologic, renal, and hepatic function and clear surgical margins for the invasive component of the tumor were required. Treatment of the axilla was at the discretion of the patient and her surgeon. Patients with hormone-receptor–positive tumors were offered tamoxifen or an aromatase inhibitor after chemotherapy. Patients had to have an expected survival of more than 5 years and no medical condition that would make treatment with this protocol unreasonably hazardous. Exclusion criteria included any other active cancer or a previous cancer with a risk of relapse that was greater than 30%.

RANDOMIZATION AND STUDY TREATMENT

Patients were randomly assigned with equal probability to standard chemotherapy or capecitabine. Standard chemotherapy consisted of either CMF or doxorubicin plus cyclophosphamide; the choice was made at the discretion of the patient or her physician. The CMF regimen consisted of cyclophosphamide, at a dose of 100 mg per square meter of body-surface area, administered orally from days 1 through 14 and methotrexate, at a dose of 40 mg per square meter, and fluorouracil, at 600 mg per square meter, administered intravenously on days 1 and 8; the cycle was repeated every 28 days for a total of six cycles. The regimen of doxorubicin plus cyclophosphamide consisted of doxorubicin, at a dose of 60 mg per square meter, and cyclophosphamide, at a dose of 600 mg per square meter, administered intravenously on day 1; the cycle was repeated every 21 days for four cycles.

The first 56 patients assigned to capecitabine received 2000 mg per square meter per day in two divided doses for 14 consecutive days every 3 weeks, for a total of six cycles, and the dose was increased to 2500 mg per square meter if they had no toxic effects after the first course. Because the toxicity of this regimen was unacceptable, the protocol was amended to eliminate the dose escalation. During the 10 weeks needed to effect this amendment, accrual continued only for the standard-chemotherapy group. Dose modifications for all regimens were based on standard NCI toxicity criteria.[18] All patients provided written informed consent that met state, federal, and institutional guidelines.

STATISTICAL ANALYSIS

The trial was designed to test the noninferiority of capecitabine as compared with standard chemotherapy by means of an adaptive Bayesian design.[19] The primary end point was relapse-free survival,

defined according to standard criteria[20] as the time from study entry until local recurrence, distant metastasis, or death from any cause, whichever occurred first. Secondary end points included overall survival (defined as the time from study entry until death from any cause), adverse events, adherence to oral chemotherapy, and quality of life and functional status.

The primary measure of efficacy was the hazard ratio for disease recurrence or death in the capecitabine group as compared with the standard-chemotherapy group. Capecitabine would be considered noninferior to standard chemotherapy if the hazard ratio was greater than 0.8046. (With the use of a 5-year landmark for descriptive purposes, this ratio corresponds to a 5-year rate of relapse-free survival of 60% for standard chemotherapy and 53% for capecitabine.) The planned sample size was 600 to 1800 patients. Interim monitoring for futility and noninferiority was planned after the enrollment of 600, 900, 1200, and 1500 patients. Noninferiority and futility bounds were defined according to Bayesian predictive probabilities with the use of noninformative prior distributions[19] for the true treatment effects. These interim analyses were not the standard type in which the trial results are announced when a boundary is crossed. Rather, the decision to discontinue enrollment was based on a prediction that future follow-up was likely to give a meaningful answer. Enrollment was to be discontinued because of predicted futility if the probability of a hazard ratio of less than 0.8046 was at least 80% after 600 patients had been enrolled, at least 70% after 900 patients had been enrolled, and at least 60% after 1200 or 1500 patients had been enrolled. Noninferiority would be established at any of these times if the probability of a hazard ratio of more than 0.8046 was at least 99%.

For the primary comparison of treatments, we used proportional-hazards modeling, adjusting for tumor size, number of involved lymph nodes, and hormone-receptor status (estrogen-receptor–positive, progesterone-receptor–positive, or both estrogen-receptor–negative and progesterone-receptor–negative). To determine the statistical significance of each variable included in the models, we used the corresponding Wald chi-square tests. Estimates of relapse-free survival and overall survival were calculated with the use of the Kaplan–Meier product-limit technique.[21] Efficacy analyses were based on the intention-to-treat principle and included all patients who were assigned to treatment. Safety evaluations included all reported adverse events and serious adverse events according to the NCI Common Toxicity Criteria.[18] Unless otherwise specified, reported P values are two-sided.

Since the benefits of improvements in chemotherapy are largely limited to patients with estrogen-receptor–negative tumors and positive lymph nodes,[22] we compared the efficacy of capecitabine with that of standard chemotherapy in patients with hormone-receptor–positive tumors and in those with hormone-receptor–negative tumors. This unplanned post hoc analysis was not described in the protocol. In testing for an interaction between treatment and hormone-receptor status, we compared capecitabine in patients who had hormone-receptor–negative tumors with all other study groups combined (i.e., capecitabine in patients with hormone-receptor–positive tumors and standard therapy in patients with hormone-receptor–positive and hormone-receptor–negative tumors). No other post hoc subgroup analyses were performed.

The CALGB Breast Cancer and Cancer in the Elderly committees designed the study. Standard-chemotherapy drugs were purchased by the patients, and capecitabine was supplied by the NCI. Data were collected by the CALGB operations office and analyzed by the CALGB statisticians. The lead author and biostatistician coauthors wrote the manuscript, which was reviewed by all the authors, and vouch for the completeness and accuracy of the data.

RESULTS

CONDUCT OF THE TRIAL

The trial opened on September 15, 2001. The first per-protocol analysis, in November 2006, after the enrollment of 600 patients, revealed 16 recurrences, distant metastases, or death from any cause in the standard-chemotherapy group and 24 in the capecitabine group. At the time, the hazard ratio for disease recurrence in the standard-chemotherapy group as compared with the capecitabine group was 0.53. In view of the small number of events, however, this hazard ratio was uncertain. Still, the Bayesian probability of a hazard ratio of less than 0.8046 was 96%, which exceeded the limit of 80% that was based on the predictive probability that after additional follow-up, the results would clearly favor futility. The data and safety monitoring board permanently closed the trial

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Standard Chemotherapy (N=326)	Capecitabine (N=307)	P Value
	no. of patients (%)		
Age			
65–69 yr	112 (34)	110 (36)	0.90†
70–79 yr	200 (61)	183 (60)	
≥80 yr	14 (4)	14 (5)	
Performance score			
0 or 1 (fully active or minimal symptoms)	317 (97)	295 (96)	0.42†
2 (symptoms, but active >50% of the time)	9 (3)	12 (4)	
Race or ethnic group			
White	277 (85)	261 (85)	0.44†‡
Black	43 (13)	29 (9)	
Hispanic	0	0	
Asian	2 (1)	4 (1)	
Other	1 (<1)	3 (1)	
Multiracial	0	1 (<1)	
Missing data	3 (1)	9 (3)	
Tumor size			
≤2 cm	159 (49)	120 (39)	0.04†
>2 to ≤5 cm	146 (45)	169 (55)	0.09§
>5 cm	18 (6)	17 (6)	
Missing data	3 (1)	1 (<1)	
No. of positive lymph nodes			
0	90 (28)	95 (31)	0.58†
1–3	179 (55)	156 (51)	0.42§
4–9	39 (12)	42 (14)	
≥10	15 (5)	13 (4)	
Missing data	3 (1)	1 (<1)	
Tumor grade			
Low	46 (14)	36 (12)	0.48†
Intermediate	124 (38)	132 (43)	
High	130 (40)	126 (41)	
Missing data	26 (8)	13 (4)	
Hormone-receptor status			
Negative	106 (33)	97 (32)	0.78†
Positive	218 (67)	209 (68)	
Missing data	6 (2)	1 (<1)	
ER and PR status			
ER-negative, PR-negative	106 (33)	97 (32)	0.37†
ER-positive, PR-negative	40 (12)	53 (17)	
ER-negative, PR-positive	6 (2)	5 (2)	
ER-positive, PR-positive	171 (52)	150 (49)	
Missing data	3 (1)	2 (1)	

Table 1. (Continued.)

Characteristic	Standard Chemotherapy (N=326)	Capecitabine (N=307)	P Value
	no. of patients (%)		
HER2 status			
Negative	246 (75)	232 (76)	0.53†
Positive	35 (11)	30 (10)	
Unknown	45 (14)	45 (15)	
Type of surgery			
Lumpectomy and breast irradiation	152 (47)	136 (44)	0.59†
Mastectomy	171 (52)	167 (54)	
Missing data	3 (1)	4 (1)	
Axillary evaluation			
Sentinel-node biopsy only	60 (18)	66 (21)	0.54†
Axillary dissection only	116 (36)	102 (33)	
Both sentinel-node biopsy and axillary dissection	147 (45)	136 (44)	
Neither sentinel-node biopsy nor axillary dissection	1 (<1)	1 (<1)	
Missing data	2 (1)	1 (<1)	

* Standard chemotherapy consisted of cyclophosphamide, methotrexate, and fluorouracil or doxorubicin plus cyclophosphamide. Percentages may not sum to 100 because of rounding. ER denotes estrogen receptor, HER2 human epidermal growth factor receptor type 2, and PR progesterone receptor.
† The P value is based on contingency-table analysis for categorical variables.
‡ The P value is for the comparison of white versus black versus all other races and ethnic groups. Race or ethnic group was self-reported.
§ The P value is based on the Mann–Whitney nonparametric test for continuous variables.

on December 29, 2006, after a total enrollment of 633 patients. We performed all statistical analyses of data available as of May 2008. The median follow-up was 2.4 years, and the maximum follow-up was 5.6 years.

Randomization was suspended during the 10-week period when the protocol was amended for capecitabine toxicity. The 19 patients enrolled during this period were all assigned to standard chemotherapy. Analyses including and excluding these patients showed no substantive differences (data not shown). All patients were included in this analysis.

PATIENTS

Of the 633 enrolled patients, 326 were randomly assigned to standard chemotherapy (133 chose CMF, 184 chose doxorubicin plus cyclophosphamide, and 9 withdrew before choosing a regimen) and 307 were randomly assigned to capecitabine; 13 patients (9 in the standard-chemotherapy group and 4 in the capecitabine group) never received the assigned therapy. Table 1 lists the characteristics of the patients. The two groups were balanced except for a slight imbalance in tumor size (P=0.04). Approximately two thirds of the patients were 70 years of age or older, and about 5% were 80 years of age or older. Most had an excellent performance status (i.e., they were ambulatory and without symptoms), 11% were black, two thirds had hormone-receptor–positive tumors, 10% had HER2-positive tumors, and 70% had positive lymph nodes; about half the tumors were more than 2 cm in diameter. The protocol was amended in 2006 to recommend trastuzumab therapy for patients with HER2-positive tumors; 8 of the 10 patients with HER2-positive disease who were subsequently enrolled received trastuzumab.

SURVIVAL

Table 2 shows the rates of relapse-free survival, relapse, overall survival, and death, as well as the causes of death. At a median follow-up of 2.4 years, the rates of both relapse and death in the capecitabine group were nearly twice those in the standard-chemotherapy group. The most common

Table 2. Outcomes at a Median Follow-up of 2.4 Years.*

Outcome	Standard Chemotherapy (N=326)	Capecitabine (N=307)
	no. of patients (%)	
Relapse-free survival		
Alive without relapse	291 (89)	247 (80)
Relapse, first occurrence	35 (11)	60 (20)
Local	5 (2)	19 (6)
Distant metastasis†	15 (5)	24 (8)
Died from any cause	15 (5)	17 (6)
Overall survival		
Alive	302 (93)	269 (88)
Died	24 (7)	38 (12)
From breast cancer	8 (2)	18 (6)
From treatment-related cause	0	2 (1)
From cause other than breast cancer or treatment	12 (4)	14 (5)
From unknown cause	4 (1)	4 (1)

* Standard chemotherapy consisted of cyclophosphamide, methotrexate, and fluorouracil or doxorubicin plus cyclophosphamide.
† This category includes four patients with synchronous local and distant relapse.

cause of death in the capecitabine group was breast cancer (in 18 of 38 patients [47%]), whereas in the standard-chemotherapy group the most common causes of death were other cancer or cardiovascular disease (in 12 of 24 patients [50%]). Table 3 shows the results of the multivariate analysis. The treatment group was significantly predictive of relapse-free survival, even after adjusting for tumor size, the number of positive lymph nodes, and hormone-receptor status. In this model, based on 622 patients, of whom 16% had disease recurrence, the hazard ratio for recurrence in the capecitabine group was twice that in the standard-chemotherapy group (hazard ratio, 2.09; P<0.001). In addition, a larger tumor, a larger number of positive nodes, and a negative hormone-receptor status were associated with a significantly higher risk of relapse (P=0.05, P=0.004, and P<0.001 for the three comparisons, respectively). Figure 1A shows the Kaplan–Meier plot of relapse-free survival according to treatment group, without adjustment for other clinical variables.

Table 3 also shows results of the multivariate model of overall survival. After adjustment for standard covariates, patients assigned to capecitabine had a risk of death that was nearly twice that for patients who were assigned to standard chemotherapy (hazard ratio, 1.85; P=0.02). As compared with smaller tumors and hormone-receptor–positive tumors, larger tumors and hormone-receptor–negative tumors were associated with significantly shorter survival (P=0.02 and P<0.001, respectively). Figure 1B shows a Kaplan–Meier plot of overall survival according to treatment group. Estimates of relapse-free survival and overall survival at 3 years indicate the advantage of standard chemotherapy, as compared with capecitabine (relapse-free survival, 85% vs. 68%; overall survival, 91% vs. 86%). We have not directly compared doxorubicin plus cyclophosphamide with CMF because these regimens were not randomly assigned. However, the comparisons of capecitabine with doxorubicin plus cyclophosphamide or CMF are qualitatively the same (data not shown).

Figure 1C through 1F shows the comparison of the benefits of capecitabine with those of standard chemotherapy in women with hormone-receptor–positive tumors and in those with hormone-receptor–negative tumors. The interaction between treatment and hormone-receptor status in this post hoc analysis was significant for both relapse-free survival and overall survival. Among patients with hormone-receptor–negative tumors who received capecitabine, the risk of relapse was more than quadrupled (hazard ratio, 4.39; 95% confidence interval [CI], 2.9 to 6.7; P<0.001), and the risk of death was more than tripled (hazard ratio, 3.76; 95% CI, 2.23 to 6.34; P<0.001), as compared with patients in all other study groups combined. There was no significant interaction between treatment group and relapse-free survival or overall survival for patients with hormone-receptor–positive tumors.

TOXICITY

Table 4 shows the incidence of grade 3, 4, and 5 adverse events that were possibly, probably, or definitely related to treatment. There were two drug-related deaths in the capecitabine group. Of the patients who received CMF, 70% had at least one grade 3 or grade 4 adverse event, as compared with 60% of patients who received doxorubicin plus cyclophosphamide and 34% of patients who received capecitabine. Among patients who received CMF or doxorubicin plus cyclophosphamide, 52% and 54%, respectively, had hematologic grade 3 or grade 4 toxic effects, but only 2% of the capecitabine group had such toxic effects. A nonhematologic grade 3 or grade 4 adverse event occurred

in 41% of patients who received CMF, 25% of those who received doxorubicin plus cyclophosphamide, and 33% of those who received capecitabine. Two patients receiving doxorubicin plus cyclophosphamide required red-cell transfusions. Congestive heart failure developed in one patient receiving CMF and in none of the patients receiving doxorubicin plus cyclophosphamide; myelodysplasia developed in one patient receiving capecitabine. A total of 62% of the patients in the CMF group, 92% of the patients in the doxorubicin–cyclophosphamide group, and 80% of the patients in the capecitabine group received all planned cycles of treatment.

In a preplanned substudy, capecitabine adherence was assessed in 161 patients using pill bottles with microelectronic monitoring. Adherence was defined as the number of doses taken divided by the number of doses planned. Compliance was defined as receipt of 80% or more of planned doses. Of these patients, 76% took more than 80% of the planned doses and 14% took 60 to 79% of the planned doses. The clinical characteristics of these patients were similar to those of the patients in the entire capecitabine population. Age was not related to adherence.[22]

Table 3. Results of Multivariate Analysis of Relapse-free and Overall Survival among 622 Patients.*

Variable	Hazard Ratio (95% CI)	P Value
Relapse-free survival		
Treatment (capecitabine vs. standard therapy)	2.09 (1.38–3.17)	<0.001
Tumor size (5 cm vs. 2 cm)	1.47 (1.00–2.15)	0.05
No. of positive lymph nodes (4 vs. 1)	1.35 (1.10–1.67)	0.004
Hormone-receptor status (negative vs. positive)	3.04 (2.02–4.57)	<0.001
Overall survival		
Treatment (capecitabine vs. standard chemotherapy)	1.85 (1.11–3.08)	0.02
Tumor size (5 cm vs. 2 cm)	1.75 (1.11–2.76)	0.02
No. of positive lymph nodes (4 vs. 1)	1.22 (0.94–1.57)	0.13
Hormone-receptor status (negative vs. positive)	2.62 (1.58–4.35)	<0.001

* A total of 11 patients were excluded because of missing data. Hazard ratios shown for relapse-free survival are for disease recurrence (16% of the patients had a recurrence or died), and hazard ratios for overall survival are for death (10% of the patients died).

DISCUSSION

This trial shows that standard adjuvant chemotherapy with either CMF or doxorubicin plus cyclophosphamide is superior to capecitabine in older women with early-stage breast cancer. The benefit of standard chemotherapy was pronounced in women with hormone-receptor–negative tumors. Most patients had substantial toxic effects. Only 62% of the patients who were assigned to CMF could complete the six planned cycles, whereas 80% of the patients who were assigned to capecitabine completed the six planned cycles. Although doxorubicin plus cyclophosphamide had substantial toxicity, 92% of the patients completed four cycles, and there were no reports of major cardiac events or leukemia. Patients in this trial had an excellent performance status and no major organ dysfunction. The toxicity of these regimens in vulnerable or frail patients is probably greater than the toxicity observed in the patients in this study, and they should be administered with caution or not at all in such patients.

Ours is one of the few trials that have focused on adjuvant chemotherapy in older women with breast cancer. A previous adjuvant trial involving older women showed that the addition of epirubicin to tamoxifen was associated with significant improvement in relapse-free survival but not overall survival, as compared with tamoxifen alone.[23] Adjuvant trials involving women younger than 70 years of age have compared the use of multiagent chemotherapy with the use of single agents and shown the superiority of multiagent chemotherapy.[7] We chose capecitabine as the single agent because it is effective when given orally and is similar, if not superior, to CMF in metastatic breast cancer.[17] Since large randomized trials have shown that adjuvant CMF and doxorubicin plus cyclophosphamide have similar efficacy,[24,25] allowing a choice of standard chemotherapy made our trial attractive to patients and physicians.

An unplanned subgroup analysis showed that the major benefits of standard chemotherapy occurred in patients with hormone-receptor–negative tumors. This finding was consistent with the Oxford Overview, which showed major benefits of chemotherapy in women with hormone-receptor–negative tumors, irrespective of age,[26] and with our previous observation that improvements in chemotherapy are noted largely in patients with hormone-receptor–negative tumors.[27]

Some flexibility in trial design is important for older patients, who have been consistently underrepresented in randomized trials of cancer chemotherapy[28,29]; age bias remains a major factor in clinical trials.[30,31] Our trial used an adaptive Bayes-

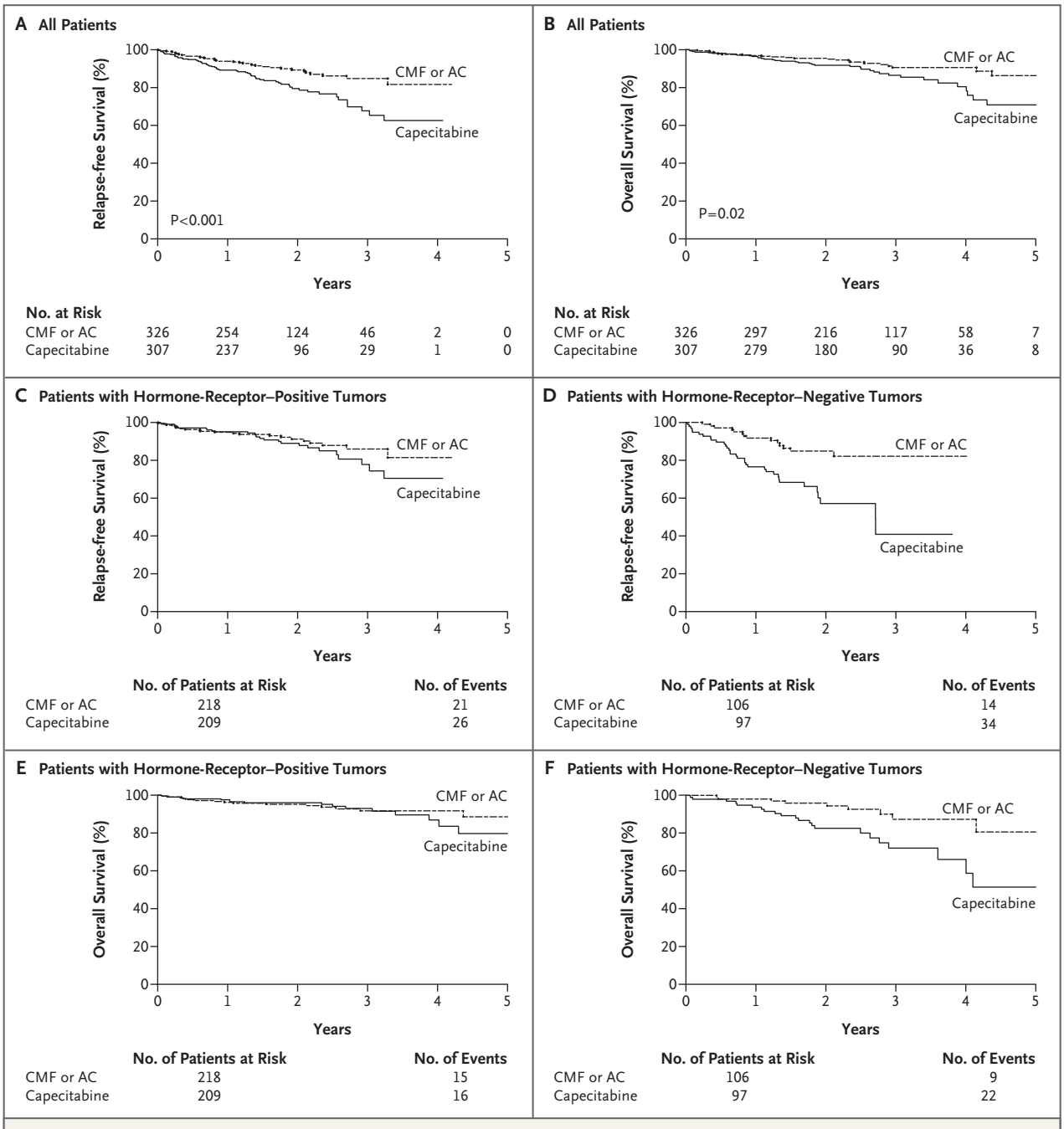

Figure 1. Kaplan–Meier Estimates of Relapse-free and Overall Survival According to Treatment Group.

Relapse-free survival (Panel A) and overall survival (Panel B) for all patients are shown. Panel C shows relapse-free survival for patients with hormone-receptor–positive tumors, and Panel D shows relapse-free survival for patients with hormone-receptor–negative tumors. Panel E shows overall survival for patients with hormone-receptor–positive tumors, and Panel F shows overall survival for patients with hormone-receptor–negative tumors. AC denotes doxorubicin plus cyclophosphamide, and CMF cyclophosphamide, methotrexate, and fluorouracil.

ian statistical design, which, together with planned sample sizes, allowed us to determine noninferiority with a relatively small sample while retaining substantial power; this design has been used successfully in other drug-evaluation trials.[19]

Our results provide support for the belief that adjuvant chemotherapy improves survival among older women. Indeed, a retrospective analysis of four randomized CALGB trials that compared less aggressive chemotherapy with more aggressive

Table 4. Grade 3, 4, or 5 Adverse Events.*

Adverse Event	CMF (N=132)	Doxorubicin plus Cyclophosphamide (N=183)	Capecitabine (N=299)
		no. of patients (%)	
Death	0	0	2 (1)†
≥1 Event	92 (70)	109 (60)	101 (34)
≥1 Hematologic adverse event	68 (52)‡	99 (54)	7 (2)
Hematologic adverse event			
Anemia	4 (3)	7 (4)	2 (1)
Requirement for transfusions	0	2 (1)	0
Leukopenia	53 (40)	79 (43)	3 (1)
Neutropenia	35 (27)	59 (32)	5 (2)
Thrombocytopenia	5 (4)	7 (4)	1 (<1)
≥1 Nonhematologic adverse event	53 (40)‡	44 (24)	98 (33)
Nonhematologic adverse event			
Fatigue	15 (11)	8 (4)	15 (5)
Mucositis	2 (2)	8 (4)	3 (1)
Nausea	9 (7)	8 (4)	6 (2)
Vomiting	8 (6)	3 (2)	6 (2)
Diarrhea	10 (8)	5 (3)	20 (7)
Hand–foot skin reaction	1 (<1)	0	47 (16)
Febrile neutropenia	11 (8)	16 (9)	2 (1)
Thrombus or embolism	5 (4)	4 (2)	3 (1)

* Grades of adverse events were defined according to the Common Toxicity Criteria of the National Cancer Institute. Listed are adverse events in all patients who received at least one dose of a drug. There were no reports of toxic effects in two patients in the standard-chemotherapy group and in four patients in the capecitabine group. Anemia was defined as a hemoglobin level of less than 8 g per deciliter. Leukopenia was defined as a white-cell count of less than 2×10^9 per liter. Neutropenia was defined as a granulocyte count of less than 1×10^9 per liter. Thrombocytopenia was defined as a platelet count of less than 50×10^9 per liter. CMF denotes cyclophosphamide, methotrexate, and fluorouracil.
† One death was from colitis, and one death was from infection.
‡ Since patients could have more than one type of adverse event, the sum of individual adverse events is larger than both the combined hematologic and nonhematologic categories and the overall total.

chemotherapy for node-positive breast cancer showed that the more aggressive therapy significantly improved relapse-free survival and overall survival, irrespective of age.[12] However, toxicity was greater in older patients.[11] Other studies have shown higher rates of cardiac toxicity[32] and secondary leukemia[33] in older patients receiving anthracycline-based regimens. Newer nonanthracycline regimens should be considered when the cardiac toxicity of anthracyclines is a major concern.[34]

Older women are more likely to be treated with lower doses of chemotherapy than are younger women,[35] yet trials of adjuvant chemotherapy for breast cancer have suggested a threshold effect for dosing.[36,37] We used doses of CMF and doxorubicin plus cyclophosphamide that have proven efficacy. For the treatment of older patients, the choice of chemotherapeutic agents, dose, schedule, and dose modification should be based on the treatment plans in published reports. Our data are part of a developing body of evidence that the choice of adjuvant chemotherapy really matters in older women with breast cancer and that standard chemotherapy is superior to the oral agent capecitabine.

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APPENDIX

The following cooperative groups participated in the CALGB study: *Eastern Cooperative Oncology Group, Philadelphia:* R.L. Comis; *Southwest Oncology Group, San Antonio, TX:* L.H. Baker; *North Central Cancer Treatment Group, Rochester, MN:* J. Buckner; *The National Surgical Adjuvant Breast and Bowel Project, Pittsburgh:* N. Wolmark; *National Cancer Institute of Canada, Toronto:* E. Eisenhauer; *Radiation Therapy Oncology Group, Philadelphia:* W.J. Curran, Jr. The following CALGB institutions participated in this study: *University of Oklahoma, Oklahoma City:* H. Ozer; *Christiana Care Health Services Community Clinical Oncology Program (CCOP), Wilmington, DE:* S. Grubbs; *Dana–Farber Cancer Institute, Boston:* E.P. Winer; *Dartmouth Medical School, Norris Cotton Cancer Center, Lebanon, NH:* M.S. Ernstoff; *Duke University Medical Center, Durham, NC:* J. Crawford; *Evanston Northwestern Healthcare CCOP, Evanston, IL:* D.L. Grinblatt; *Grand Rapids Clinical Oncology Program, Grand Rapids, MI:* M. Lange; *Greenville CCOP, Greenville, SC:* J.K. Giguere; *Cancer Center of Carolinas Hematology-Oncology Associates of Central New York CCOP, Syracuse:* L.J. Kirshner; *Illinois Oncology Research Association, Peoria:* J.W. Kugler; *Long Island Jewish Medical Center, Lake Success, NY:* K.R. Rai; *Memorial Sloan-Kettering Cancer Center, New York:* C.A. Hudis; *Missouri Baptist Medical Center, St. Louis:* A.P. Lyss; *Missouri Valley Consortium CCOP, Omaha, NE:* G.S. Soori; *Mount Sinai Medical Center, Miami:* R.C. Lilenbaum; *Mount Sinai School of Medicine, New York:* L.R. Silverman; *Nevada Cancer Research Foundation CCOP, Las Vegas:* J.A. Ellerton; *New Hampshire Oncology-Hematology PA, Concord:* D.J. Weckstein; *Northern Indiana Cancer Research Consortium CCOP, South Bend:* R. Ansari; *Roswell Park Cancer Institute, Buffalo, NY:* E. Levine; *Sibley Memorial Hospital, Washington, DC:* F.P. Smith; *Southeast Cancer Control Consortium CCOP, Greensboro, NC:* J.N. Atkins; *State University of New York Upstate Medical University, Syracuse:* S.L. Graziano; *the Ohio State University Medical Center, Columbus:* C.D. Bloomfield; *University of California at San Diego, La Jolla:* B.A. Parker; *University of Chicago, Chicago:* G. Fleming; *University of Illinois CCOP, Chicago:* L.E. Feldman; *University of Iowa, Iowa City:* D.A. Vaena; *University of Maryland Greenebaum Cancer Center, Baltimore:* M. Edelman; *University of Massachusetts Medical School, Worcester:* W.V. Walsh; *University of Minnesota, Minneapolis:* B.A. Peterson; *University of Missouri/Ellis Fischel Cancer Center, Columbia:* M.C. Perry; *University of Vermont, Burlington:* H.B. Muss; *Wake Forest University School of Medicine, Winston-Salem, NC:* D.D. Hurd; *Walter Reed Army Medical Center, Washington, DC:* T. Reid; *Washington University School of Medicine, St. Louis:* N. Bartlett; *Weill Medical College of Cornell University, New York:* J. Leonard; *Western Pennsylvania Cancer Institute, Pittsburgh:* R.K. Shadduck.

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Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial

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Summary

Background Elderly and frail patients with cancer, although often treated with chemotherapy, are under-represented in clinical trials. We designed FOCUS2 to investigate reduced-dose chemotherapy options and to seek objective predictors of outcome in frail patients with advanced colorectal cancer.

Methods We undertook an open, 2×2 factorial trial in 61 UK centres for patients with previously untreated advanced colorectal cancer who were considered unfit for full-dose chemotherapy. After comprehensive health assessment (CHA), patients were randomly assigned by minimisation to: 48-h intravenous fluorouracil with levofolinate (group A); oxaliplatin and fluorouracil (group B); capecitabine (group C); or oxaliplatin and capecitabine (group D). Treatment allocation was not masked. Starting doses were 80% of standard doses, with discretionary escalation to full dose after 6 weeks. The two primary outcome measures were: addition of oxaliplatin ([A *vs* B]+[C *vs* D]), assessed with progression-free survival (PFS); and substitution of fluorouracil with capecitabine ([A *vs* C]+[B *vs* D]), assessed by change from baseline to 12 weeks in global quality of life (QoL). Analysis was by intention to treat. Baseline clinical and CHA data were modelled against outcomes with a novel composite measure, overall treatment utility (OTU). This study is registered, number ISRCTN21221452.

Findings 459 patients were randomly assigned (115 to each of groups A–C, 114 to group D). Factorial comparison of addition of oxaliplatin versus no addition suggested some improvement in PFS, but the finding was not significant (median 5·8 months [IQR 3·3–7·5] *vs* 4·5 months [2·8–6·4]; hazard ratio 0·84, 95% CI 0·69–1·01, p=0·07). Replacement of fluorouracil with capecitabine did not improve global QoL: 69 of 124 (56%) patients receiving fluorouracil reported improvement in global QoL compared with 69 of 123 (56%) receiving capecitabine. The risk of having any grade 3 or worse toxic effect was not significantly increased with oxaliplatin (83/219 [38%] *vs* 70/221 [32%]; p=0·17), but was higher with capecitabine than with fluorouracil (88/222 [40%] *vs* 65/218 [30%]; p=0·03). In multivariable analysis, fewer baseline symptoms (odds ratio 1·32, 95% CI 1·14–1·52), less widespread disease (1·51, 1·05–2·19), and use of oxaliplatin (0·57, 0·39–0·82) were predictive of better OTU.

Interpretation FOCUS2 shows that with an appropriate design, including reduced starting doses of chemotherapy, frail and elderly patients can participate in a randomised controlled trial. On balance, a combination including oxaliplatin was preferable to single-agent fluoropyrimidines, although the primary endpoint of PFS was not met. Capecitabine did not improve QoL compared with fluorouracil. Comprehensive baseline assessment holds promise as an objective predictor of treatment benefit.

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See Comment page 1725

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Introduction

Advanced colorectal cancer is the second most common cause of death from cancer in developed countries, after lung cancer.[1,2] In the UK, the median age at death from advanced colorectal cancer is 77 years, with 60% of deaths occurring in patients older than 75 years and 42% in those older than 80 years.[3] Frailty, whether or not related to the cancer diagnosis, is frequent in elderly patients.

Standard treatment for advanced colorectal cancer includes palliative chemotherapy, with an expanding range of treatment options. But the evidence supporting these treatments is from clinical trials that under-represented elderly, frail, and especially frail elderly patients.[4] Several pivotal trials were restricted to patients younger than 75 years;[5–7] however, even without a formal upper age limit there are several impediments to the recruitment of elderly participants.[8] Reports of outcomes in older[4] or frailer[9] patient subsets within these trials, although interesting, are limited by the fact that the participants were by definition sufficiently robust to have been included in the trials in the first place, whereas many other patients were not.

In 2002, the UK Medical Research Council (MRC) noted that investigators of its first-line trial for advanced colorectal cancer, FOCUS (Fluorouracil, Oxaliplatin, CPT11 [irinotecan]: Use and Sequencing),[10] despite permissive

entry criteria and no upper age limit, were recruiting patients with a median age of only 64 years. A survey of investigators showed that the 59 trial oncologists who responded, while recruiting 422 patients into FOCUS, had treated a further 715 patients off-trial during the same period, frequently using reduced-dose or single-agent schedules. The most common reasons cited for non-inclusion of technically eligible patients were physicians' concerns about the adverse effects of standard-dose treatments, patients' wishes to avoid toxic effects, and an assumption that oral therapy would improve quality of life (QoL). We therefore designed FOCUS2 for patients with advanced colorectal cancer who were to receive chemotherapy, but for whom the treating oncologist considered standard full-dose regimens to be unsuitable.

Methods

Study design and patients

Three trial design innovations were used to make FOCUS2 suitable for the frail and elderly population to be studied. First, as is common in non-trial practice, cytotoxic drugs were started at below-standard doses; second, a comprehensive geriatric health assessment was used to identify factors that might aid future selection of patients or regimens; third, alongside standard outcome measures a composite measure of overall treatment utility (OTU) was devised, incorporating objective and subjective measures of benefit and harm.

FOCUS2 was undertaken in 61 UK centres, recruiting patients between January, 2004, and July, 2006. To enter FOCUS2, the oncologist had first to confirm, stating reasons, that the patient was in his or her opinion not a candidate for standard full-dose combination therapy. Patients had to have histologically confirmed colorectal adenocarcinoma, with unidimensionally measurable inoperable advanced or metastatic disease, and a WHO performance status of 2 or better. Patients had to have received no previous systemic chemotherapy for metastases. There was no upper or lower age limit. Previous adjuvant chemotherapy was allowed if completed more than 4 months before randomisation; previous rectal chemoradiotherapy was allowed if completed more than 1 month before randomisation. Patients were not excluded for medical comorbidity unless the condition was so severe as to preclude protocol treatment. However, the following criteria were required: white blood cell count 3×10^9 per L or greater, platelet count 100×10^9 per L or greater, serum bilirubin no more than three times the upper limit of normal (ULN), serum transaminases no more than 2·5 times ULN, and glomerular filtration rate (GFR) 30 mL per min or greater.

We obtained written consent after verbal explanation and a written information sheet had been given to the patient, with at least 24 h allowed for consideration. Thereafter, but before randomisation, a 117-item comprehensive health assessment (CHA) was done (webappendix pp 1–8). This assessment comprised four nurse-administered modules (physical parameters including timed 20-m walk,[11] mini-nutritional assessment,[12] mini-mental state examination,[13] and medical comorbidity[14]) and four patient-completed modules (activities of daily living,[15] symptoms,[16] anxiety or depression,[17] and global QoL or health resources[18]).

See Online for webappendix

FOCUS-2 was approved by national and institutional research ethics committees and undertaken by the MRC Clinical Trials Unit (CTU), with MRC Good Clinical Research Practice,[19] and was overseen by an independent Trial Steering Committee. Confidential interim analyses were reviewed every year by an independent Data Monitoring Committee.

Randomisation and masking

Patients were randomly assigned in a 1:1:1:1 ratio by telephone with a computerised algorithm developed and maintained centrally at the MRC CTU. Randomisation was done by use of the method of minimisation stratified by clinician, WHO performance status, status of primary tumour (resected or not), and age. Treatment allocation was not masked.

Procedures

Treatment was started with standard regimens but at 80% of standard cytotoxic drug doses. Group A received levofolinate 175 mg 2-h intravenous infusion, fluorouracil 320 mg/m² 5-min intravenous bolus, and fluorouracil 2240 mg/m² 46-h intravenous infusion. The cycle was repeated every 14 days (FU regimen). This regimen is 80% of the simplified LV5FU2 regimen used in FOCUS.[10,20] Group B received levofolinate 175 mg/m² and oxaliplatin 68 mg/m² by concurrent 2-h intravenous infusion, fluorouracil 320 mg/m² 5-min intravenous bolus, and fluorouracil 1920 mg/m² 46-h intravenous infusion. The cycle was repeated every 14 days (OxFU regimen). This regimen is 80% of the simplified FOLFOX regimen in FOCUS.[10,20] Group C received capecitabine 1000 mg/m² orally twice per day on days 1–15. The cycle was repeated every 21 days (Cap regimen). This regimen is 80% of the standard licensed schedule. Group D received oxaliplatin 104 mg/m² 2-h intravenous infusion, and capecitabine 800mg/m² orally twice per day on days 1–15. The cycle was repeated every 21 days (OxCap regimen). This regimen is 80% of the standard XELOX regimen.[21] In patients with GFR 30–50 mL per min, oxaliplatin and capecitabine were further reduced by 25%.

Before each cycle, toxicity was scored with common terminology criteria for adverse events (version 3.0). Detailed management of side-effects was specified; briefly, grade 1 and worse effects were treated symptomatically; persisting grade 2 and worse toxicity at day 1 of the next treatment cycle incurred a 1-week delay. Cytotoxic doses were reduced by 20% after two delays, or one delay of 2 weeks or more. If grade 2 or worse transaminitis (>2·5 times ULN) developed during capecitabine therapy, treatment was held until recovery.

For grade 3 hyperbilirubinaemia (>3 times ULN), all cytotoxic drugs were reduced by 50%. Oxaliplatin was omitted for persistent grade 2 and worse neurological toxic effects. Compliance with capecitabine was assessed with patient diary cards and tablet returns.

A senior clinician assessment was scheduled after 6 weeks, when doses could be escalated to 100% of standard doses (an increase of 25% of starting doses), provided that no grade 2 or worse non-haematological toxic effects had occurred and that the patient assented. After week 12, radiological response was assessed with Response Evaluation Criteria In Solid Tumors (RECIST) criteria;[22] the clinician assessed whether there had been clinical deterioration in the patient; the CHA was repeated (omitting the comorbidity and mental-state modules) and the patient was asked two additional questions: whether their treatment had been worthwhile and how much it had interfered with activities (webappendix pp 9–13).

Thereafter, patients without radiological or clinical evidence of deterioration could continue the same regimen, immediately or after a planned break, with reassessment every 12 weeks. In groups A and C, when progression occurred on the FU or Cap regimens, second-line treatment was considered with the OxFU or OxCap regimens, respectively. Second-line therapy in groups B and D, and third-line therapy in all groups, was at the discretion of the physician.

Statistical analysis

The primary questions in the two factorial comparisons were: does oxaliplatin improve first-line progression-free survival (PFS; [A *vs* B]+[C *vs* D])?; and does substitution of fluorouracil with capecitabine improve global QoL ([A *vs* C]+[B *vs* D])?

For the first question, PFS was defined as time from randomisation to first progression or death from any cause, assessed by intention to treat. FOCUS2 was designed to detect a 3-month improvement in median PFS from 6 months to 9 months. For 90% power at the two-sided 5% significance level, 460 patients were needed.

For the second question, the primary outcome was QoL improvement. This outcome was defined as any increase between baseline and 12 weeks in the EORTC-QLQ-C30 global QoL subscale, reported as a percentage of patients with baseline and 12-week data. In a previous MRC trial,[23] 40% of 117 patients reported improved global QoL with this criterion. Paired data from 260 patients (57% of the total) would be sufficient to detect an increase from 40% to 60%, at the two-sided 5% significance level, with 90% power. PFS was a secondary outcome for this comparison.

Secondary outcome measures for both comparisons included response rate (RR), toxic effects, and overall survival (OS). For time-to-event endpoints, Kaplan-Meier curves were produced with patients alive and event-free being censored at the time last seen. Hazard ratios (HRs)

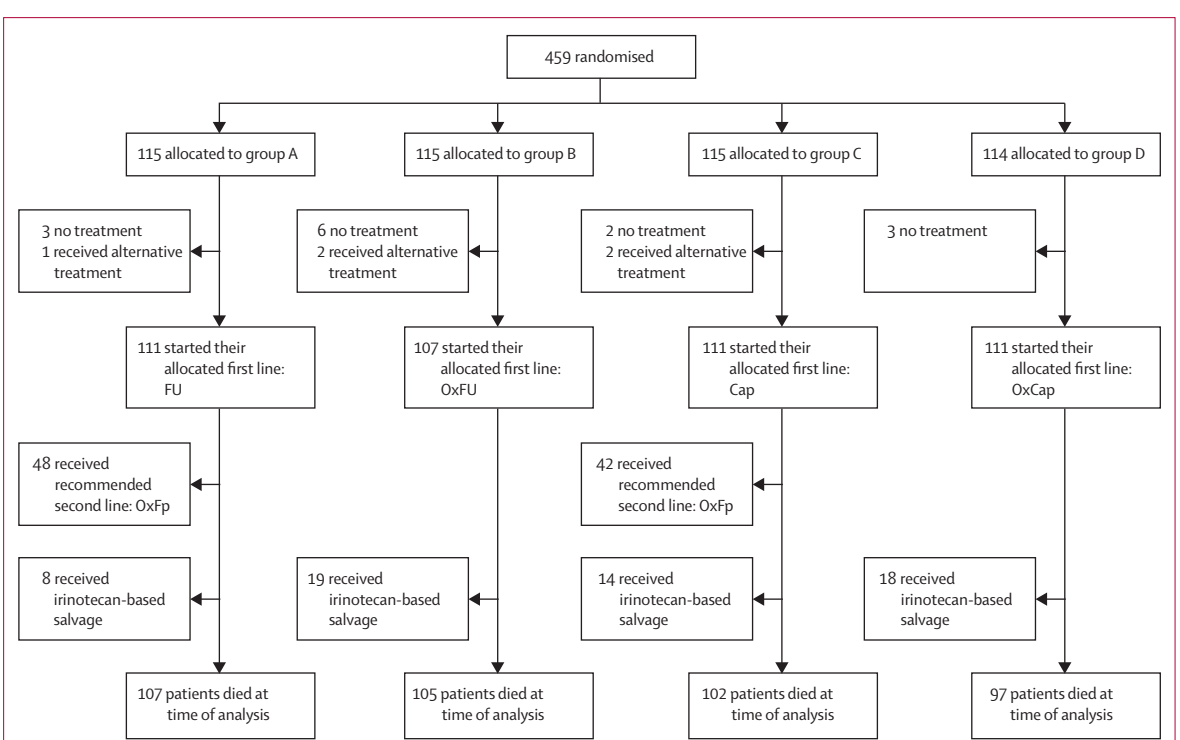

Figure 1: **Trial profile**
FU=simplified LV5FU2 regimen of levofolinate, bolus fluorouracil, and 46-h infusion of fluorouracil, repeated every 2 weeks. OxFU=oxaliplatin plus FU. Cap=capecitabine. OxCap=oxaliplatin plus Cap. OxFp=oxaliplatin plus fluoropyrimidine (either fluorouracil or capecitabine).

	Group A (n=115)	Group B (n=115)	Group C (n=115)	Group D (n=114)	Total (n=459)
Sex					
Men	73 (63%)	69 (60%)	68 (59%)	68 (60%)	278 (61%)
Women	42 (37%)	46 (40%)	47 (41%)	46 (40%)	181 (39%)
Age (years)					
Median	75	75	73	75	74
IQR	71–78	71–78	69–78	70–79	70–78
Range	46–86	35–87	49–84	45–85	35–87
WHO performance status					
0	25 (22%)	23 (20%)	23 (20%)	27 (24%)	98 (21%)
1	58 (50%)	57 (50%)	58 (50%)	54 (47%)	227 (50%)
2	32 (28%)	35 (30%)	34 (30%)	33 (29%)	134 (29%)
Primary tumour site					
Rectum	25 (22%)	30 (26%)	31 (27%)	34 (30%)	120 (26%)
Colon	90 (78%)	85 (74%)	84 (73%)	80 (70%)	339 (74%)
Primary tumour not resected	39 (34%)	40 (35%)	40 (35%)	40 (35%)	159 (35%)
Metastatic sites					
No distant metastases	1 (1%)	2 (2%)	1 (1%)	1 (1%)	5 (1%)
Non-liver metastases	31 (27%)	25 (22%)	30 (26%)	26 (23%)	112 (24%)
Liver-only metastases	17 (15%)	14 (12%)	14 (12%)	22 (19%)	67 (15%)
Liver+other metastases	66 (57%)	74 (64%)	70 (61%)	65 (57%)	275 (60%)
Reason for entering FOCUS2					
Advanced age alone	35 (30%)	28 (24%)	37 (32%)	35 (31%)	135 (29%)
Frailty/patient choice alone	37 (32%)	36 (31%)	35 (30%)	40 (35%)	148 (32%)
Both age and frailty/choice	43 (37%)	51 (44%)	43 (37%)	39 (34%)	176 (38%)

Data are number (%), unless otherwise indicated.

Table 1: **Baseline patient characteristics**

	Group A	Group B	Group C	Group D
Allocated first-line treatment	FU	OxFU	Cap	OxCap
Number allocated	115	115	115	114
Number started treatment	111	107	111	111
Dose escalation at 6 weeks				
On study at 6 weeks	100	106	107	106
Dose escalated	47 (47%)	36 (34%)	39 (36%)	32 (30%)
Eligible for escalation but not escalated	31 (31%)	41 (39%)	30 (28%)	33 (31%)
Not escalated because of toxicity	16 (16%)	23 (22%)	23 (21%)	38 (36%)
Dose delivery during first 12 weeks of treatment				
Increased at 6 weeks and sustained	20 (18%)	14 (13%)	11 (10%)	15 (14%)
Sustained starting dose	32 (29%)	32 (30%)	42 (38%)	40 (36%)
Further dose reduced or stopped	57 (51%)	59 (55%)	54 (48%)	46 (41%)
Higher dose than intended*	2 (2%)	2 (2%)	4 (4%)	10 (9%)

Data are number (%), unless otherwise indicated. FU=simplified LV5FU2 regimen of levofolinate, bolus fluorouracil, and 46-h infusion of fluorouracil, repeated every 2 weeks. OxFU=oxaliplatin plus FU. Cap=capecitabine. OxCap=oxaliplatin plus Cap. *These patients had a dose increase earlier than the protocol-specified week 6 escalation point.

Table 2: **Treatment received**

and 95% CIs were calculated for each comparison and compared with stratified log-rank tests. RR and toxic effects are reported as percentage of assessable patients and compared with χ^2 tests. We compared QoL improvement with the Mann-Whitney test, which allows for non-normality. Tests for heterogeneity were done for time-to-event outcomes and tests of interaction for all other outcomes.

The novel composite measure OTU was devised to reflect whether, from the viewpoint of both patient and clinician and with use of both objective and subjective measures, the treatment had been worthwhile. OTU was scored at 12 weeks (webappendix p 14). Briefly, good OTU indicated no clinical or radiological evidence of disease progression, and no major negative treatment effects in terms of toxicity or patient acceptability. Intermediate OTU signified either clinical deterioration but no negative treatment effect, or a significant negative treatment effect but no clinical deterioration. Poor OTU indicated both clinical deterioration and a major negative treatment effect, or death.

We then investigated whether baseline clinico-pathological and CHA data can help to predict the probability of a favourable OTU at 12 weeks. Categorical factors and continuous factors with predefined cutoffs for categories were treated as categorical, with all other variables regarded as continuous. Univariate analyses were first done, with ordinal logistic regression, to assess patients' baseline characteristics and CHA data in relation to the OTU score at 12 weeks. All variables, irrespective of their univariate result, were then included in a multivariable analysis with backward stepwise ordinal logistic regression. Results are displayed with odds ratios (ORs) to show the odds of a worse outcome, with effect size (Z value) and statistical significance (p value).

This study is registered, number ISRCTN21221452.

Role of the funding source

The sponsor of the study was the MRC which, as the parent body of the MRC CTU, was involved in the design, conduct, and analysis of the trial. The manufacturers of the drugs used in the study were not involved in the research. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 411 of 459 (90%) patients had died at the time of final analysis. Baseline characteristics were well balanced between groups (table 1). Median age was 74 years (range 35–87), with 199 (43%) patients older than 75 years and 60 (13%) older than 80 years. 98 (21%) patients had WHO performance status of 0, 227 (49%) a performance status of 1, and 134 (29%) a performance status of 2. The reason for inclusion in FOCUS2 instead of a full-dose protocol was cited as frailty in 324 (71%) patients and advanced age in 311 (68%). However, dementia was uncommon: full baseline mini-mental health data were obtained in 387 patients, of whom 374 (96%) scored within the normal range and only two (0·5%) fell within the range associated with dementia.

419 (91%) patients were alive and receiving treatment 6 weeks after starting treatment, and so were eligible for discretionary escalation to 100% of standard doses (table 2). Of these patients, 154 (37%) had dose escalation. Dose escalation was more frequent in patients allocated single agent than combination therapy (p=0·01).

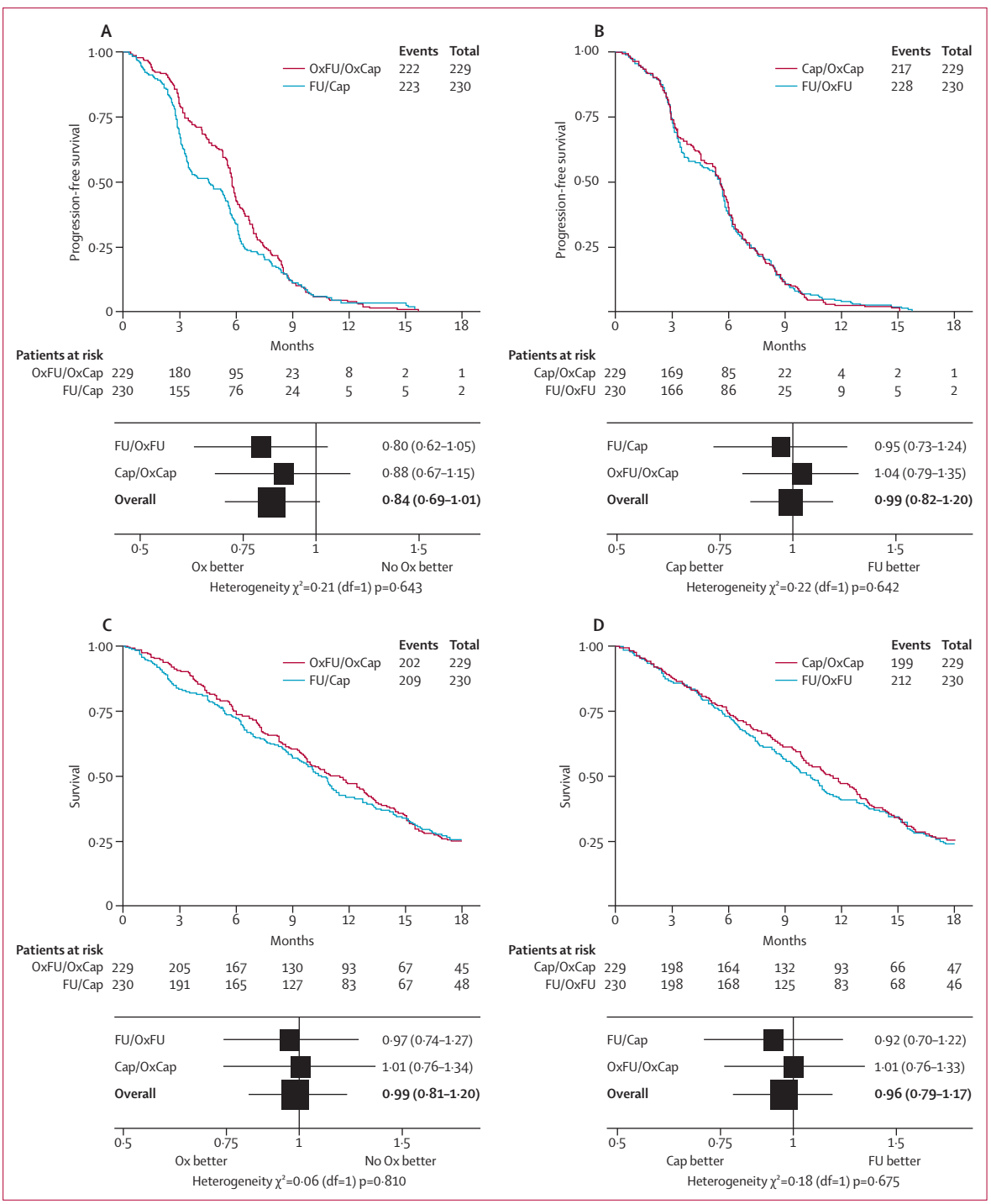

Figure 2: **Kaplan-Meier curves for PFS and OS for each main effect comparison and hazard ratio plots to show tests for heterogeneity for each factorial comparison**

(A) PFS by addition of oxaliplatin. (B) PFS by FU versus Cap. (C) OS by addition of oxaliplatin. (D) OS by FU versus Cap. PFS=progression-free survival. OS=overall survival. FU=simplified LV5FU2 regimen of levofolinate, bolus fluorouracil, and 46-h infusion of fluorouracil, repeated every 2 weeks. OxFU=oxaliplatin plus FU. Cap=capecitabine. OxCap=oxaliplatin plus Cap.

	Individual groups				Factorial comparisons					
					Addition of oxaliplatin [A *vs* B] + [C *vs* D]			Fluorouracil *vs* capecitabine [A *vs* C] + [B *vs* D]		
	A (FU)	B (OxFU)	C (Cap)	D (OxCap)	No oxaliplatin	With oxaliplatin	p	Fluorouracil based	Capecitabine based	p
Number allocated	115	115	115	114	230	229	..	230	229	..
Survival and response										
Number started treatment	111	107	111	111	222	219	..	218	222	..
RECIST response at week 12–14										
Response rate: CR + PR (%)*	12 (11%)	41 (38%)	16 (14%)	36 (32%)	28 (13%)	77 (35%)	<0·0001	53 (24%)	52 (23%)	0·83
Disease control: CR + PR + SD (%)	51 (46%)	76 (71%)	56 (50%)	72 (65%)	107 (48%)	148 (68%)	<0·0001	127 (58%)	128 (58%)	0·90
Median PFS (months; IQR)†	3·5 (2·8–6·2)	5·8 (3·2–7·6)	5·2 (2·8–6·7)	5·8 (3·3–7·4)	..	..	..	..	..	..
HR (95% CI)	..	..	..	..	Reference	0·84 (0·69–1·01)	0·07	Reference	0·99 (0·82–1·20)	0·93
Median OS (months; IQR) †	10·1 (5·1–17·3)	10·7 (5·7–17·2)	11·0 (5·4–18·0)	12·4 (5·8–18·0)	..	..	..	..	..	..
HR (95% CI)	..	..	..	..	Reference	0·99 (0·81–1·18)	0·91	Reference	0·96 (0·79–1·17)	0·71
Improved QoL at week 12–14										
Complete QoL data	62	62	65	58	127	120	..	124	123	..
Improved global QoL (%)	37 (60%)	32 (52%)	42 (65%)	27 (47%)	79 (62%)	59 (49%)	0·04	69 (56%)	69 (56%)	0·94
OTU score at 12 weeks										
Assessable for OTU	109	107	111	111	220	218	..	216	222	
Good (%)	38 (35%)	58 (54%)	41 (37%)	45 (41%)	79 (36%)	103 (47%)	0·003‡	96 (44%)	86 (39%)	0·27‡
Intermediate (%)	37 (34%)	29 (27%)	33 (30%)	41 (37%)	70 (32%)	70 (32%)	..	66 (31%)	74 (33%)	..
Poor (%)	34 (31%)	20 (19%)	37 (33%)	25 (23%)	71 (32%)	45 (21%)	..	54 (25%)	62 (30%)	..

FU=simplified LV5FU2 regimen of levofolinate, bolus fluorouracil, and 46-h infusion of fluorouracil, repeated every 2 weeks. OxFU=oxaliplatin plus FU. Cap=capecitabine. OxCap=oxaliplatin plus Cap. RECIST=Response Evaluation Criteria In Solid Tumors. CR=complete response. PR=partial response. SD=stable disease. PFS=progression-free survival. OS=overall survival. QoL=quality of life. OTU=overall treatment utility. *Interaction test: Z=–1·18, p=0·238. †Interaction tests done for time-to-event endpoints (figure 2) and OTU score. ‡χ^2 test for trend.

Table 3: **Main outcome measures**

Only 60 (14% of all patients starting treatment) sustained the higher dose to 12 weeks (table 2). 146 (33%) patients sustained the 80% standard starting dose to 12 weeks, whereas 215 (49%) needed a further dose reduction or stopped (table 2). Capecitabine compliance, assessed by tablet returns, was greater than 97% in the Cap (group C) and OxCap (group D) regimens (data not shown).

At the time of analysis 445 (97%) patients had had a PFS event (figure 2A). PFS, measured by intention to treat, was the primary outcome measure for the factorial comparison of treatment with or without oxaliplatin; this comparison suggested some benefit of oxaliplatin but the finding was not significant (figure 2A; table 3). Factorial comparison of fluorouracil versus capecitabine showed no effect on PFS (figure 2B; table 3).

Paired baseline and 12-week QoL data were available in 247 patients, with similar numbers in each group (table 3). QoL improvement was the primary outcome measure for the factorial comparison of fluorouracil versus capecitabine; this comparison showed no difference between groups, with more than half of assessable patients reporting improved QoL in both groups (table 3). Factorial comparison of treatment with and without oxaliplatin was suggestive of a detrimental effect with oxaliplatin regimens (table 3).

RR was assessed with RECIST criteria but only at 12 weeks after randomisation. In the factorial comparisons, we recorded good evidence that oxaliplatin increased the RR (complete response plus partial response) and the rate of disease control (stable disease, complete response, and partial response; table 3). We noted no evidence that the substitution of fluorouracil with capecitabine had an effect on response or disease control (table 3).

Factorial analysis showed no evidence of OS benefit with first-line oxaliplatin (figure 2C). Similarly, factorial analysis showed no difference in OS between fluorouracil and capecitabine (figure 2D).

440 (96%) patients had complete data for toxic effects. The overall risk of having a grade 3 or worse event during the first 12 weeks ranged from 27% of assessed patients (29 of 109) with the FU regimen to 43% (47 of 110) with the OxCap regimen (table 4). In the factorial comparisons, the use of oxaliplatin did not significantly increase the overall risk of toxic effects, but we noted evidence of increased rates of diarrhoea, neurosensory toxicity, nausea, vomiting, and neutropenia, and a lower rate of hand-foot syndrome compared with no use of oxaliplatin (table 4). Compared with fluorouracil, capecitabine increased the overall risk of a grade 3 or worse event (p=0·03), and was specifically associated with increased rates of nausea, vomiting, diarrhoea, anorexia, and hand-foot syndrome.

438 (95%) patients had complete data to allow scoring of OTU at 12 weeks, of whom 182 (42%) scored good, 140 (32%) intermediate, and 116 (26%) poor. Better OTU

	Group A (FU; N=109)	Group B (OxFU; N=109)	Group C (Cap; N=112)	Group D (OxCap; N=110)	Factorial comparisons			
					Addition of oxaliplatin		Fluorouracil *vs* capecitabine	
					[A *vs* B] + [C *vs* D]	p	[A *vs* C] + [B *vs* D]	p
Any toxicity								
Grade ≥2	84 (77%)	81 (74%)	86 (77%)	94 (86%)	170 (77%) *vs* 175 (80%)	0·45	165 (76%) *vs* 180 (81%)	0·17
Grade ≥3	29 (27%)	36 (33%)	41 (37%)	47 (43%)	70 (32%) *vs* 83 (38%)	0·17	65 (30%) *vs* 88 (40%)	0·03
Nausea								
Grade ≥2	8 (7%)	17 (16%)	15 (13%)	27 (25%)	23 (10%) *vs* 44 (44%)	<0·0001	25 (12%) *vs* 42 (19%)	0·03
Grade ≥3	1 (1%)	2 (2%)	6 (5%)	5 (5%)	7 (3%) *vs* 7 (3%)	0·99	3 (1%) *vs* 11 (5%)	0·03
Vomiting								
Grade ≥2	5 (5%)	13 (12%)	12 (11%)	21 (19%)	17 (8%) *vs* 34 (16%)	0·01	18 (8%) *vs* 33 (15%)	0·03
Grade ≥3	1 (1%)	2 (2%)	3 (3%)	3 (3%)	4 (2%) *vs* 5 (2%)	0·73	3 (1%) *vs* 6 (3%)	0·33
Anorexia								
Grade ≥2	12 (11%)	15 (14%)	19 (17%)	26 (24%)	31 (14%) *vs* 41 (19%)	0·18	27 (12%) *vs* 45 (20%)	0·03
Grade ≥3	3 (3%)	3 (3%)	6 (5%)	4 (4%)	9 (4%) *vs* 7 (3%)	0·62	6 (3%) *vs* 10 (5%)	0·33
Stomatitis								
Grade ≥2	12 (11%)	13 (12%)	6 (5%)	12 (11%)	18 (8%) *vs* 25 (11%)	0·25	25 (12%) *vs* 18 (8%)	0·24
Grade ≥3	2 (2%)	3 (3%)	1 (1%)	2 (2%)	3 (1%) *vs* 5 (2%)	0·47	5 (2%) *vs* 3 (1%)	0·46
Diarrhoea								
Grade ≥2	20 (18%)	21 (19%)	23 (21%)	38 (35%)	43 (20%) *vs* 59 (27%)	0·06	41 (19%) *vs* 61 (28%)	0·03
Grade ≥3	5 (5%)	7 (6%)	10 (9%)	20 (18%)	15 (7%) *vs* 27 (12%)	0·05	12 (6%) *vs* 30 (14%)	0·003
Lethargy								
Grade ≥2	41 (38%)	46 (42%)	40 (36%)	47 (43%)	81 (37%) *vs* 93 (43%)	0·21	89 (40%) *vs* 87 (39%)	0·88
Grade ≥3	8 (7%)	10 (9%)	15 (13%)	16 (15%)	23 (10%) *vs* 26 (12%)	0·63	18 (8%) *vs* 31 (14%)	0·06
Pain								
Grade ≥2	17 (16%)	18 (17%)	24 (21%)	20 (18%)	41 (19%) *vs* 38 (17%)	0·74	35 (16%) *vs* 44 (20%)	0·30
Grade ≥3	9 (8%)	5 (5%)	11 (10%)	6 (6%)	20 (9%) *vs* 11 (5%)	0·10	14 (6%) *vs* 17 (8%)	0·61
Neurosensory								
Grade ≥2	2 (2%)	10 (9%)	4 (4%)	15 (14%)	6 (3%) *vs* 25 (11%)	0·0005	12 (6%) *vs* 19 (9%)	0·21
Grade ≥3	0 (0%)	1 (1%)	0 (0%)	4 (4%)	0 (0%) *vs* 5 (2%)	0·02	1 (1%) *vs* 4 (2%)	0·18
HFS								
Grade ≥2	1 (1%)	2 (2%)	24 (21%)	13 (12%)	25 (11%) *vs* 15 (7%)	0·10	3 (1%) *vs* 37 (17%)	<0·0001
Grade ≥3	0 (0%)	0 (0%)	11 (10%)	2 (2%)	11 (5%) *vs* 2 (1%)	0·01	0 (0%) *vs* 13 (6%)	0·0001
Platelets								
Grade ≥2	0 (0%)	2 (2%)	1 (1%)	2 (2%)	1 (0·5%) *vs* 4 (2%)	0·17	2 (1%) *vs* 3 (1%)	0·67
Grade ≥3	0 (0%)	1 (1%)	1 (1%)	1 (1%)	1 (0·5%) *vs* 2 (1%)	0·56	1 (0·5%) *vs* 2 (1%)	0·57
Anaemia								
Grade ≥2	20 (18%)	21 (19%)	14 (13%)	18 (16%)	34 (15%) *vs* 39 (18%)	0·49	41 (19%) *vs* 32 (14%)	0·22
Grade ≥3	3 (3%)	3 (3%)	1 (1%)	2 (2%)	4 (2%) *vs* 5 (2%)	0·73	6 (3%) *vs* 3 (1%)	0·30
Neutropenia								
Grade ≥2	6 (6%)	11 (10%)	3 (3%)	10 (9%)	9 (4%) *vs* 21 (10%)	0·02	17 (8%) *vs* 13 (6%)	0·42
Grade ≥3	3 (3%)	6 (6%)	2 (2%)	2 (2%)	5 (2%) *vs* 8 (4%)	0·39	9 (4%) *vs* 4 (2%)	0·15

Tests for interaction between the two treatment factors showed no evidence of an interaction (data not shown). FU=simplified LV5FU2 regimen of levofolinate, bolus fluorouracil, and 46-h infusion of fluorouracil, repeated every 2 weeks. OxFU=oxaliplatin plus FU. Cap=capecitabine. OxCap=oxaliplatin plus Cap. HFS=hand-foot syndrome.

Table 4: **Toxic effects, weeks 1–12**

was strongly associated with improved PFS and OS (both p<0·0001, log-rank trend test; data not shown). In the factorial comparisons, allocation to receive oxaliplatin was associated with better OTU (p=0·003), but we recorded no significant difference in OTU with fluorouracil or capecitabine (table 3).

Univariate analysis was done with baseline clinicopathological variables, CHA variables, and treatment allocation (figure 3). The strongest predictors of 12-week OTU were: WHO performance status, white blood cell count, EQ5D QoL score, overall symptom score, and allocation to oxaliplatin (all p<0·01; figure 3).

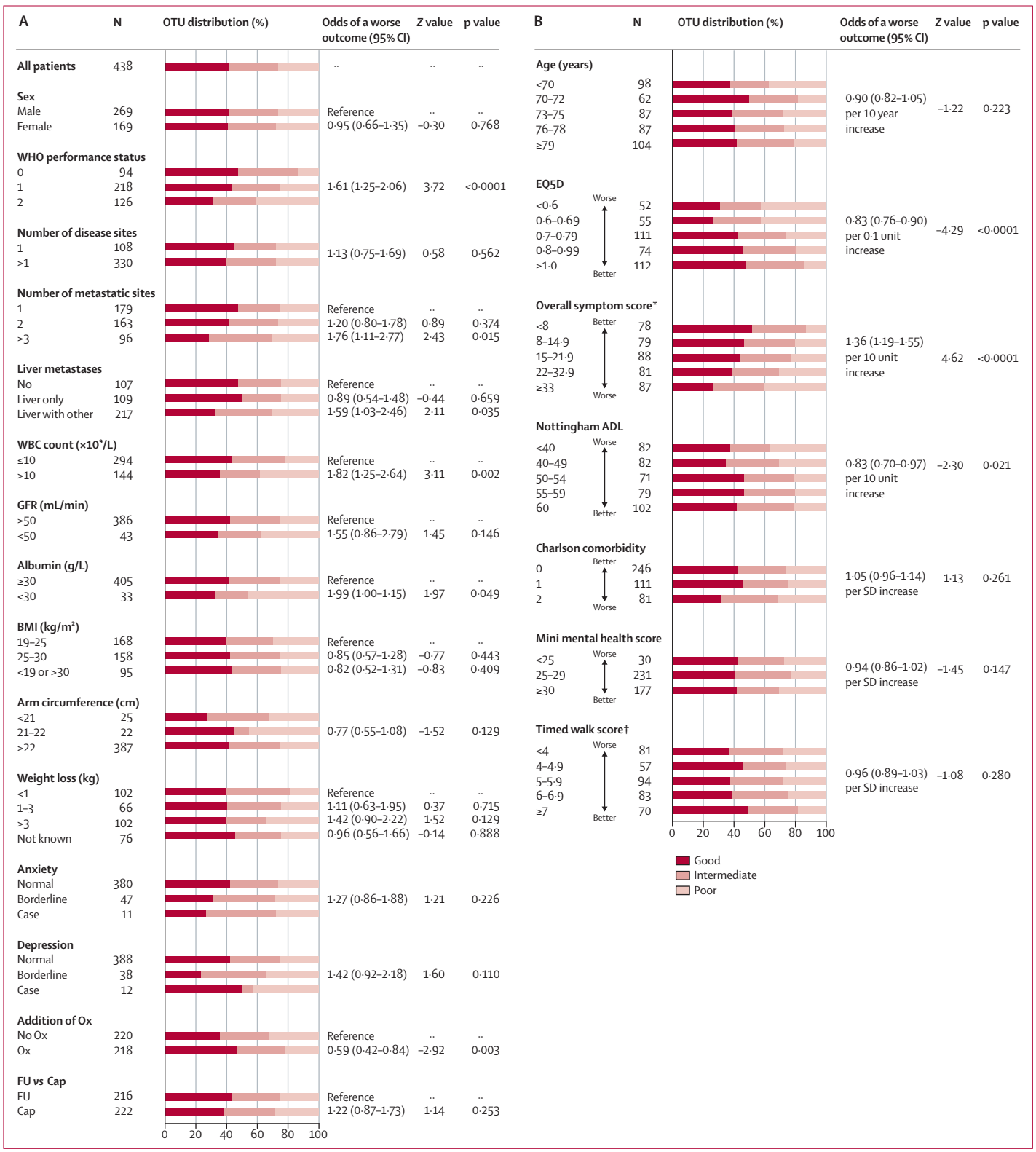

***Figure 3*: Association of categorical factors (A) and continuous factors (B) associated with OTU outcome**

Odds of a worse outcome is expressed with reference to the more normal state, or as an odds ratio proportional across all categories. OTU=overall treatment utility. WBC=white blood cell. GFR=glomerular filtration rate. BMI=body-mass index. FU=simplified LV5FU2 regimen of levofolinate, bolus fluorouracil, and 46-h infusion of fluorouracil, repeated every 2 weeks. Ox=oxaliplatin. Cap=capecitabine. ADL=activities of daily living. *Mean EORTC QLQ-C30 symptom score. †Calculated as 100/time in s to walk 20 m.

	Odds of a worse outcome (95% CI)	Z value	p value
Overall baseline symptom score	1·32* (1·14–1·52)	3·79	<0·0001
Additional oxaliplatin	0·57 (0·39–0·82)	−2·98	0·003
Liver with other metastases	1·51 (1·05–2·19)	2·22	0·026
WHO performance status	1·28 (0·96–1·70)	1·70	0·090
Age	1·00 (0·98–1·02)	0·14	0·887

Interaction between the two treatment factors was assessed (Z=−1·26, p=0·209). OTU=overall treatment utility. *This odds ratio relates to a 10-point change in the overall symptom score.

Table 5: **Factors associated with OTU outcome (multivariate analysis)**

We recorded no evidence of interaction between the two treatment factors (p=0·209; data not shown).

Multivariable analyses (table 5) produced a potentially predictive model based on overall symptom score, presence of liver plus extrahepatic metastases, and treatment. WHO performance status and age were included for clinical relevance. On the basis of this model, a 70-year-old patient with performance status of 1, with both liver and extrahepatic metastases, whose overall symptom score is 60, treated with single-agent fluoropyrimidines, has a 61% (95% CI 45–76) probability of a poor OTU and only a 12% (5–20) probability of a good OTU. Conversely, an 80-year-old patient with performance status of 1 and a symptom score 0 and either extrahepatic-only or liver-only disease, treated with combination chemotherapy, has a 66% (56–77) probability of a good OTU and only 10% (5–14) probability of a poor OTU.

Discussion

This is the largest randomised controlled trial so far to have selectively recruited frail and elderly patients with advanced colorectal cancer (panel). With use of reduced starting drug doses, adapted for this population, combination chemotherapy including oxaliplatin seems, on balance, preferable to single-agent fluoropyrimidines, although the primary endpoint of PFS was not met. We did not, however, detect any advantage of capecitabine compared with fluorouracil.

FOCUS2 successfully recruited an elderly and frail population into a large national trial. Indeed, the trial proved so popular with patients and clinicians that it recruited well ahead of target, showing that age and frailty need not be barriers to research. The decision to start treatments at 80% of standard doses, although arbitrary, mimics common non-trial practice in frail elderly patients. Generally moderate rates of toxic effects and good rates of improvement in QoL in all groups would seem to support this strategy, whereas the relatively low uptake of escalation at 6 weeks, and the fact that only 14% of all patients sustained full-dose therapy to 12 weeks, supports the notion that the trial population was unsuited for full-dose therapy.

We introduced a novel composite endpoint, OTU, to assess the outcome of palliative chemotherapy, and explored the use of objective baseline evaluation to estimate the likelihood of a good or poor outcome with treatment. When confirmed and refined with further studies, this approach could potentially provide valuable guidance for doctors and patients in the difficult decisions between active or symptomatic care or, potentially, between active regimens. The interpretation of clinical trials, especially trials of palliative chemotherapy, often needs subjective synthesis of the objective data. Measures of efficacy are weighed against toxic effects, convenience, and other variables before deciding which treatment is best. For FOCUS2 we developed a simple composite endpoint of treatment outcome, OTU, to reflect both the doctor's question: "In retrospect, am I glad I offered this treatment?"; and the patient's question: "Am I glad I accepted it?". OTU combines clinical efficacy ("Is my patient alive without disease progression?"), clinical tolerability ("Did we avoid causing major harm?"), and patient opinion ("Was my treatment worthwhile and acceptable?"). We encourage other research groups to adopt and refine this patient-centred approach.

OTU proved useful in comparison of treatment groups, particularly when conventional endpoints were divergent. The addition of oxaliplatin significantly increased RR and suggested some improvement in PFS, although this

Panel: **Research in context**

Systematic review

Previous publications and international meeting abstracts were searched with Ovid Medline and American Society of Clinical Oncology databases to find previous reports of palliative chemotherapy in elderly and frail patients with advanced colorectal cancer. Until now, the major reports of survival data for elderly patients receiving palliative chemotherapy have come from subgroup analyses of older patients participating in standard full-dose trials,[4] or from trials of full-dose chemotherapy in selected fit elderly patients.[24] These analyses show that elderly patients selected for full-dose treatments achieve survival times similar to younger patients on the same treatments; however, they represent only a small and highly selected proportion of the elderly cancer population.

Interpretation

FOCUS2 adds to the totality of evidence because it is the first large randomised trial in colorectal cancer to have been designed specifically for frail elderly patients and to relate objective baseline measures of geriatric fitness with patient-related outcomes of chemotherapy. Survival, at a median of 11 months, is noticeably shorter than in contemporaneous standard trials. For example, during overlapping recruitment periods two other MRC trials, FOCUS and COIN, were running at many of the same centres as FOCUS2, accruing patients with a median age of 63 years, more than 90% of whom had WHO performance status 0–1, with median survival of 14–17 months.[10,25,26] Meanwhile, in France, a selective trial using more intensive therapy achieved median survival of more than 20 months.[27] However, a meta-analysis of 6286 patients in nine trials, including FOCUS and the French trial, shows that frailty is a dominant negative prognostic factor, with median survival of only 8·5 months in the subpopulation with WHO performance stats of 2.[9] This finding is entirely consistent with the survival recorded in FOCUS2, in which 134 of 459 (29%) patients were of performance status 2, and 324 of 459 (71%) were regarded as too frail to receive standard therapy (table 1).

finding was not significant; however, it also increased some toxic effects and seemed to negatively affect global QoL. So overall, was treatment with oxaliplatin worthwhile? OTU showed unequivocal evidence of overall benefit with oxaliplatin (table 3; figure 3).

For the second factorial question, capecitabine has previously been shown to be non-inferior to fluorouracil,[28] and oral therapy is generally thought to be preferred by patients, either because of its convenience or because it is assumed to have low toxicity. However, although analysis of PFS and RR confirmed capecitabine's efficacy, we recorded increased toxicity and no evidence of improved QoL. And despite including a measure of whether treatment interferes with patients' normal activities, the OTU scores for patients receiving capecitabine were not superior; indeed, they tended to favour fluorouracil, although this difference was not significant (table 2B; figure 3A).

Guidelines from the US National Comprehensive Cancer Network recommend use of a comprehensive geriatric assessment (CGA) to guide decision making when considering chemotherapy in elderly patients.[29,30] However, there currently exists no evidence-based method to combine the many data items generated by the CGA into one decision about whether to offer chemotherapy, or which regimen to use. The 117-item geriatric assessment used in FOCUS2 was feasible in the oncology clinic, and we have started to identify which elements are of greatest value in prediction of the use of palliative chemotherapy. To develop a working predictive model will need cross-validation with other studies, but this approach offers the potential to better inform oncologists' discussions with patients. For example, a high predicted probability of a good OTU would support encouragement for chemotherapy; conversely, a high predicted probability of poor OTU (eg, in a patient with a high symptom score and widespread metastases) might help the oncologist and patient to consider with confidence the option of non-chemotherapy-based care.

New therapies now present new opportunities to develop treatments with few toxic effects for frail elderly patients with advanced colorectal cancer. For example, investigators of the AGITG MAX trial,[31] undertaken in patients of median age 68 years, reported significantly improved PFS without significant extra toxicity from the addition of bevacizumab to single-agent capecitabine. We encourage investigators to continue to design trials using appropriate low-toxicity treatments and patient-centred assessment to expand the evidence base in this important specialty.

Contributors

MTS was the chief investigator of the trial and participated in its design and analysis, and in preparation of the report. HSW, GM, and TSM contributed to the trial design. AEB and MSO'M advised on geriatric assessment methods. LCT, MP, and REL were responsible for data management, analysis, and interpretation, and contributed to the preparation of the report. SFS, MTS, HSW, GM, AEB, and TSM recruited patients to the trial. All authors commented on the report.

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Conflicts of interest

MTS has received travel and accommodation and departmental research funding (unconnected with FOCUS2) from Roche. HSW has received travel support, honoraria, and educational support from Roche and Sanofi-Aventis. LCT, MP, and REL are employed by the UK MRC, which is also the trial sponsor. MSO'M is the Chair the Academic and Research Committee of the British Geriatrics Society and chairs the Drugs and

Prescribing section of the British Geriatrics Society. The British Geriatrics Society has a mission statement that clinical trials be inclusive of older people and frail people. GM, AEB, SFS, and TSM declare that they have no conflicts of interest.

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ORIGINAL REPORT

Implementing a Geriatric Assessment in Cooperative Group Clinical Cancer Trials: CALGB 360401

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Clinical Trials repository link available on JCO.org.

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ABSTRACT

Purpose
Factors captured in a geriatric assessment can predict morbidity and mortality in older adults, but are not routinely measured in cancer clinical trials. This study evaluated the implementation of a geriatric assessment tool in the cooperative group setting.

Patients and Methods
Patients age ≥ 65 with cancer, who enrolled on cooperative group cancer trials, were eligible to enroll on Cancer and Leukemia Group B (CALGB) 360401. They completed a geriatric assessment tool before initiation of protocol therapy, consisting of valid and reliable geriatric assessment measures which are primarily self-administered and require minimal resources and time by healthcare providers. The assessment measures functional status, comorbidity, cognitive function, psychological state, social support, and nutritional status. The protocol specified criteria for incorporation of the tool in future cooperative group trials was based on the time to completion and percent of patients who could complete their portion without assistance. Patient satisfaction with the tool was captured.

Results
Of the 93 patients who enrolled in this study, five (5%) met criteria for cognitive impairment and three did not complete the cognitive screen, leaving 85 assessable patients (median age, 72 years). The median time to complete the geriatric assessment tool was 22 minutes, 87% of patients (n = 74) completed their portion without assistance, 92% (n = 78) were satisfied with the questionnaire length, 95% (n = 81) reported no difficult questions, and 96% (n = 82) reported no upsetting questions. One hundred percent of health care professionals completed their portion.

Conclusion
This brief, primarily self-administered geriatric assessment tool met the protocol specified criteria for inclusion in future cooperative group clinical trials.

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INTRODUCTION

The majority of cancer incidence and mortality occurs in older adults; however, clinical trials, which set the standard of care, usually accrue younger participants with a good performance status.[1-3] Since the world population is aging, and given the known association between cancer and aging,[4,5] there is a critical need to improve our evidence-based knowledge regarding the care of older adults with cancer. Several studies have demonstrated that although older adults derive similar benefit from cancer therapy as do younger patients,[6,7] they are at a greater risk for treatment toxicity.[8-11] However, aging is a heterogeneous process that is not captured by chronologic age. The domains in a geriatric assessment are designed to capture the functional age of an older adult. This identifies those older adults who have a diminished life expectancy and/or are at risk for hospitalization and functional decline.[12,13]

Emerging data support the predictive and prognostic value of a geriatric assessment in weighing the risks and benefits of cancer treatment in an older adult.[14-18] However, a traditional geriatric assessment is time consuming and has not been routinely incorporated into oncology practice or cooperative group clinical trials because of the time, resources, and expertise required to capture the information. To overcome this barrier, a brief geriatric assessment tool was designed, utilizing valid and reliable geriatric assessment measures which are primarily self-administered and require minimal resources and time by health care providers. The geriatric assessment tool included several validated

measures of functional status, comorbidity, cognitive function, psychological state, social support, and nutritional status. This geriatric assessment tool, devised in collaboration with members from the Cancer and Leukemia Group B (CALGB) Cancer in the Elderly Committee, garnered expertise from specialists in geriatrics, oncology, psychology, quality of life, health outcomes research, and biostatistics. A comprehensive review of possible tools to measure each domain was performed. The final measures included in this brief geriatric assessment were chosen for their reliability, validity, brevity, and prognostic ability to determine risk for morbidity or mortality in an older patient. The geriatric assessment tool primarily consisted of self-reported measures which were completed by the patient. Three items were completed by the health care professional. This geriatric assessment tool was developed in two stages.

The goal of the first stage was to evaluate the feasibility of the geriatric assessment tool among older patients with a cancer diagnosis of breast, lung, colorectal cancer, or lymphoma who were receiving treatment with standard of care chemotherapy. These patients were accrued from two participating sites (Memorial Sloan-Kettering Cancer Center and the University of Chicago). The mean time to completion of the geriatric assessment tool was fewer than 30 minutes. In addition, the majority of patients were able to complete the self-administered questionnaire without assistance (78%), and were satisfied with the questionnaire length (90%). We therefore concluded that the geriatric assessment was feasible in the stated setting.[19]

The goal of the second stage was to determine whether this geriatric assessment tool could be successfully implemented in the cooperative group setting and to identify any barriers to implementing the tool in the cooperative group setting. Results of this study will be used to refine the geriatric assessment tool in order to achieve a final tool that will then be incorporated within cooperative group clinical trials. This report documents the findings from the second stage of development.

PATIENTS AND METHODS

CALGB 360401 was a limited-access study opened at 15 participating CALGB institutions. The study was approved by the National Cancer Institute central institutional review board and by the institutional review board at each participating institution.

Eligibility Criteria

The eligibility criteria included age at study enrollment $\geq$ 65 years, diagnosis of malignancy, any performance status level, and enrollment in a cooperative group treatment trial but treatment not yet started. Because several measures used in the assessment tool were not validated in other languages, eligibility was restricted to patients with the ability to follow directions in English.

Geriatric Assessment Tool

The geriatric assessment tool included validated measures of geriatric assessment across the domains of functional status, comorbid medical conditions, psychological state, social support, nutritional status, cognitive function, and medications (Table 1).[20-31] A full description of the measures included in this tool has been previously reported.[19] The geriatric assessment tool was composed of a patient portion and a health care provider portion. The patient portion was composed of self-reported measures of functional status, comorbidity, psychological state, social support, nutritional status, and medications. The patient portion was designed to be completed by the patient; however, a member of the health care team assisted those who needed help. The health care provider portion consisted of three measures: rating the patient's Karnofsky performance status,[22] the Timed Up and Go[24] (a performance-based measure of the patient's functional status), and the Blessed Orientation-Memory-Concentration test[30] (a screening measure of the patient's cognitive function).

Patients reported their degree of satisfaction with the geriatric assessment tool. They were asked to comment on the length of the tool and to identify difficult or distressing items. The time to complete the entire geriatric assessment tool as well as the health care provider and patient portions were captured. The percent of patients who required assistance and the reasons for requiring assistance to complete the tool were recorded.

End Points

The study end points were: percentage of patients able to complete the patient portion of the assessment tool without assistance; length of time needed to complete the entire geriatric assessment tool; percent of patients missing at least one item on a scale; patient satisfaction with the patient portion, including identifying items that were distressing or difficult to comprehend and satisfaction with the length of the questionnaire; and percentage of health care professionals who completed their portion of the geriatric assessment tool. The end points were formulated by the CALGB Cancer in the Elderly Committee and Quality of Life. They were also reviewed by the CALGB executive committee. There was consensus among the members of these committees with regard to these end points.

Per protocol, successful implementation would be declared if: more than 70% of patients completed the self-report patient questionnaire without assistance, and the median time to complete the entire geriatric assessment tool was fewer than 40 minutes. With the aim of refining the geriatric assessment tool, a measure might be removed if: more than 25% of patients failed to answer at least one item on a geriatric assessment measure included within the tool, or more than 20% of patients reported that the measure was upsetting or difficult to understand. Also, if fewer than 80% of health care professionals completed the health care professional portion, this portion might be modified or removed from the geriatric assessment tool.

Study Implementation

The geriatric assessment tool was completed by patients before initiation of cancer treatment. The study implementation process is summarized in Figure 1. To identify potentially eligible patients at participating institutions, CALGB information systems generated a daily report of patients age $\geq$ 65 registered in a CALGB trial at each participating institution. The study principal investigator or a member of the research team reviewed this report daily and notified researchers at the participating institution of potentially eligible patients. A member of the institution's research team explained the study to the patient, and informed consent was obtained from eligible patients who agreed to participate. The study team at each institution was trained by the study principal investigator via phone on protocol procedures and delivery of the geriatric assessment. A flow chart for accrual is summarized in Appendix Figure A1 (online only). Patient registration and data collection were managed by the CALGB statistical center.

Statistical Considerations

Statistical analyses were performed by CALGB statisticians. A target sample size of 80 patients was selected so that the length of a 95% CI would be no larger than 0.20 when estimating proportions higher than 0.70. Patients were categorized into two cohorts according to age, namely, 65 to 69 and $\geq$ 70 years. Enrollment to the 65 to 69 age cohort was capped at 25% of the study cohort in order to ensure that the median age of the study cohort would be older than 70 years. Descriptive statistics, including 95% CIs, were used to summarize data from this study.

A patient's refusal to complete the Blessed Orientation-Memory-Concentration Test[30] or a score of 11 or higher was considered an indication of questionable cognitive capacity to provide accurate and reliable self-reported information. These patients were therefore excluded from all study analyses.

Table 1. Domains and Measures Captured by Geriatric Assessment Tool

Domain With Measure	No. of Items	Description
Functional status		
MOS physical health[20]	10	Measures limitations in a wide range of physical functions (from bathing/dressing to vigorous activities such as running)
Instrumental Activities of Daily Living [subscale of the OARS][21]	7	Measures ability to complete activities required to maintain independence in the community (ie, meal preparation, shopping, making telephone calls, money management)
Karnofsky performance status (rated by the health care professional)[22]*	1	Global indicator of patient function determined by the health care professional on a scale of 0 to 100
Karnofsky self-reported performance rating scale[23]	1	Global indicator of patient function determined by patient self-report ranging from normal to severely disabled on a scale of 40 to 100
No. of falls in last 6 months	1	No. of times patient has fallen in last 6 months
Timed Up and Go[24]*	1	Performance-based measure of functional status: amount of time it takes for seated patient to rise from a chair, walk 10 feet, walk back, and sit down
MOS social activities[20]	4	Measures ability to participate in social activities and degree to which health status limits normal social activities
Comorbid medical conditions		
Physical health section (subscale of the OARS)[21]	15	List of comorbid illnesses and the degree to which they impair daily activities; patient can add additional comorbid illnesses not listed; rating of eyesight and hearing
Psychological state		
Hospital Anxiety and Depression Scale[25]	14	Measures of anxiety and depression
Social support		
MOS social support survey: emotional/ information and tangible subscales[26]	12	Perceived availability of social support
Nutritional status		
Body mass index[27]	1	Weight/height^2
Percent unintentional weight loss in past 6 months[28,29]	1	Unintentional weight loss in last 6 months/baseline body weight × 100
Cognition		
Blessed Orientation-Memory-Concentration test[30,31]*	6	Gross measure of cognitive function
Medications		
Comprehensive list of medications	1	List of medications including prescribed, herbal, and over-the-counter medications

Abbreviations: MOS, Medical Outcomes Study; OARS, Older American Resources and Services.
*Items completed by the healthcare professional (Karnofsky performance status, Timed Up and Go, and Blessed Orientation-Memory-Concentration test).

RESULTS

CALGB 360401 was activated in December 2006. The protocol was subsequently approved by the institutional review board at the participating sites (institutional review board approval ranging from February 2007 to April 2008). The time to obtain institutional review board approval at the individual sites contributed to the initial lag in accrual. In June 2008, the age 65 to 69 years cohort closed to accrual with 24 patients. Accrual continued to the age 70+ years cohort until January 2009, when accrual to that cohort closed with 69 patients. The final total accrual was 93 patients. Two recruitment rates were calculated: patients successfully recruited to the study of all patients screened for eligibility: 93 of 191 (49%); and patients successfully recruited to the study out of all patients approached for consent: 93 of 120 (78%).

Of the 93 enrolled patients, three patients refused to take the Blessed Orientation-Memory-Concentration test[30] and five patients scored 11 or greater (the cutoff score for cognitive impairment). This left 85 patients assessable for analyses. The remainder of this report is based on the 85 assessable patients.

Patient demographics are summarized in Table 2. The median age of all enrolled and assessable patients was 72 (range, 65 to 90 years). Three fourths of these patients were at least 70 years of age. More than half of the patients (59%) were male; only three were nonwhite. Most (57%) patients were married. Slightly more than half (56%) of patients had at least some college background.

The median time to complete the geriatric assessment tool (patient and health care professional portion) was 22 minutes, with a minimum of 6 and a maximum of 60 minutes (Table 3). Patients took a median of 15 minutes (range, 3 to 45 minutes) to complete their portion and health care professionals took a median of 5 minutes (range, 1 to 30 minutes) to complete their portion of the geriatric assessment tool. Of the 85 assessable patients, 100% (n = 85) of the health care professionals completed their portion. The health care professional portion could be completed by the nurse, research assistant, or physician. Only 2% of physicians completed the health care professional questionnaire and the remainder was completed by the nurse and/or research assistant. Of the 85 assessable patients, 87% (n = 74; 95% CI, 78% to 93%) of patients completed their portion of the geriatric assessment tool without assistance (Table 4). The reasons cited for the 11 patients requiring assistance included visual problems (n = 3), fatigue (n = 1), and other reasons (n = 7), including general health, assistance with completing the medication list, frustration, non-English primary language, protective/controlling daughter, and request to have questionnaire read. Illiteracy and item difficulty were not mentioned as a reason for requiring assistance. These results meet the protocol-specified criteria to declare feasibility.

Table 4 shows the degree of patient satisfaction with the self-administered questionnaire. Seventy-eight patients (92%) were satisfied with the questionnaire length, five patients (6%) felt it was long, and two patients (2%) did not respond. Eighty-one patients (95%)

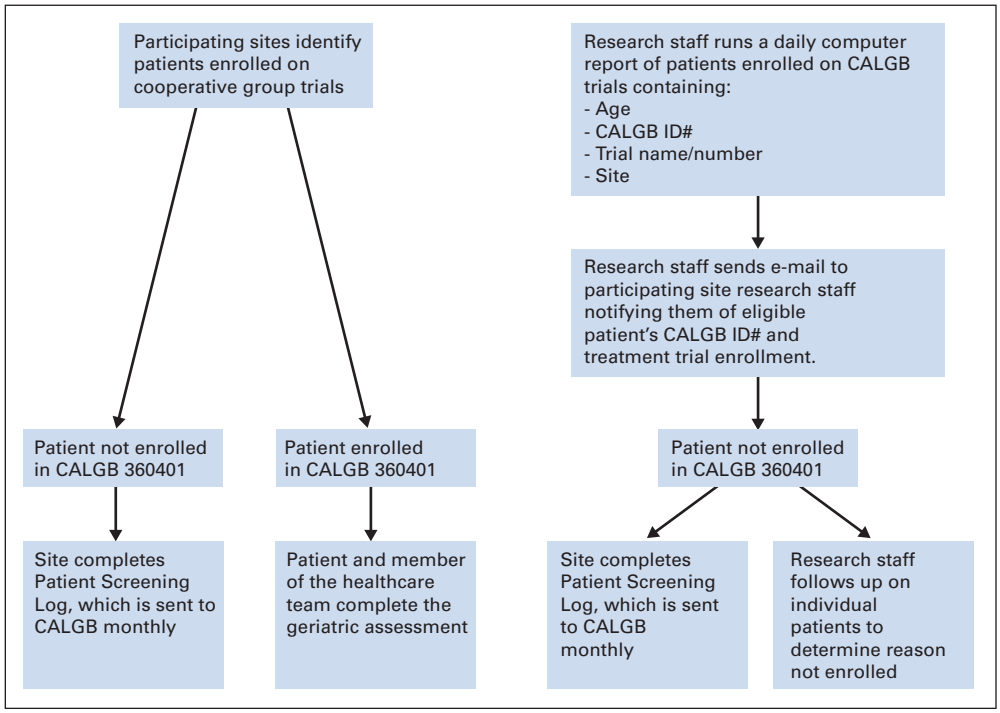

Fig 1. Cancer and Leukemia Group B (CALGB) 360401 flow chart of procedures.

said there were no difficult questions; four patients (5%) reported difficult questions, citing the social support items specifically. Eighty-two patients (96%) were not upset by any questions, two patients (2%) reported the mood and social support questions upsetting, and one patient (1%) did not reply to this question.

The number of missing items for each measure in the geriatric assessment was calculated. More than 90% of patients completed all items on their questionnaires (Table 5). Results of the geriatric assessment are summarized in Table 5. Fifteen patients (18%) required assistance with instrumental activities of daily living, 17 patients (19%) reported at least one fall in the previous 6 months; 25 patients (29%) reported $\geq$ three comorbid illnesses; 20 patients (24%) reported fair or poor hearing, and 47 patients (55%) reported taking five or more medications. Only three patients (3%) scored above the threshold for anxiety/depression on the Hospital Anxiety and Depression Scale.[25] Fifteen patients (18%) had greater than 5% unintentional weight loss, and 15 patients (18%) had a body mass index lower than 22 kg/m^2.

DISCUSSION

Approximately 60% of cancer diagnoses and 70% of cancer mortality occur in patients age $\geq$ 65.[32] Studies have demonstrated that older adults have been under-represented in cancer clinical trials, although more recent data suggest that these statistics are starting to improve.[33,34] Because characteristics other than age of older adults enrolled in these trials are not routinely captured, there is a dearth of knowledge regarding the factors other than age that identify vulnerable older adults at risk for treatment toxicity. We studied the feasibility of implementing a geriatric assessment in the cooperative group setting. Previously described barriers to incorporating a geriatric assessment in oncology care included the required time and resources. Therefore, we developed a geriatric assessment tool that could be largely self-administered with minimal provider time involved.

The rationale for the inclusion of a geriatric assessment in cooperative group clinical trials is several fold. First, since aging is a heterogeneous process, factors covered by a geriatric assessment, other than chronological age, can provide researchers with information on the overall baseline status of older individuals enrolled in their clinical trials.[27,28,35-43] This information gives investigators an opportunity to account for factors other than cancer that put the older patient at risk for morbidity and mortality. Second, inclusion of a geriatric assessment provides a descriptor of the individuals enrolled on the clinical trial. Therefore, physicians in practice can have a better understanding of whether the patients included on the clinical trial have similar characteristics to the patients who they are treating in daily clinical practice. Most importantly, the geriatric assessment provided clinical information that might otherwise go unrecognized. For example, 5% of the patients enrolled on this study scored above threshold for cognitive impairment on the memory test, and these patients had signed consent to participate in a cooperative group treatment trial. This information was reported to the treating physicians so that they could determine whether any further neurologic work-up was needed. Finally, inclusion of a geriatric assessment in clinical trials could potentially identify the factors which predispose older patients to treatment toxicity. This information would be used as the basis for developing the next generation of clinical trials for vulnerable older adults that would incorporate interventions or novel treatment approaches to decrease the risk of treatment toxicity.

Several geriatric assessments have been proposed in the literature.[17,44-46] Most include the domains described in this geriatric assessment, and the authors acknowledge that any of these

Table 2. Patient Characteristics

Characteristic	Patients No.	Patients %
Assessable patients	85	100
Age, years		
65-69	21	25
70-74	34	40
≥ 75	30	35
Sex		
Female	35	41
Male	50	59
Cancer type		
Breast	12	14
Prostate	22	26
Lymphoma	11	13
Lung	12	14
GI	13	15
Leukemia/myeloma	8	9
Melanoma	2	2
Endometrium	2	2
Other	3	4
Cancer stage		
I	6	7
II	17	20
III	15	18
IV	43	51
Other*	4	5
Educational level		
Less than high school	9	11
High school graduate	27	32
Any college	28	33
Any post-college	20	24
Missing	1	1
Marital status		
Married	48	57
Widowed	21	25
Single	7	8
Separated, divorced, other	9	11
Employment status		
Full or part-time	14	16
Retired, homemaker, unemployed	70	82
Other	1	1
Household composition		
Lives alone	23	27
Lives with spouse, partner, or child	62	73
Race		
White	82	96
Black	0	0
Hispanic	1	1
Asian	1	1
Multiracial	1	1

*Other includes three patients with leukemia and one patient with limited-stage small-cell lung cancer.

Table 3. Time to Complete the Geriatric Assessment

Statistic (minutes)	Instrument: Health Care Professional Questionnaire	Instrument: Patient Questionnaire	Instrument: Composite Assessment Tool
Mean	7	17	24
Standard deviation	5	7	10
Median	5	15	22*
Range	1-30	3-45	6-60

NOTE. N = 85.
*Median time to complete both the health care professional questionnaire and patient questionnaire for a given subject, and not the summation of median times for completing each questionnaire separately.

approaches would be reasonable. However, inclusion of uniform measures across studies would increase the ease and applicability of cross-study comparison, and validate the assessment's predictive capabilities. The geriatric assessment tool described in this article includes validated and reliable measures, is primarily self-administered, requires little health care provider time and resources for completion, and was acceptable in length and in content to most patients. Nurses and research assistants primarily completed the health care provider portion. The assessment includes measures that capture a broad range of physical function as individuals who are seeking cancer treatment or treatment on clinical trial may be healthier than the general geriatric population. Furthermore, this assessment was easily incorporated into a cooperative group setting.

There are limitations to this geriatric assessment tool. It is brief and therefore may miss subtle findings that a more comprehensive assessment might detect. In addition, some items require a health care provider's attention; however, the time required to complete these items is brief. The time intervals to complete the assessment were self-reported, and the validity needs to be considered in that context; however, the average times to completion are reported as medians so that the degree of under- or over-reporting by individuals would have lesser impact. Furthermore, although patient satisfaction with the geriatric assessment tool was captured, the health care provider's satisfaction was not captured. Although most of the measures are self-explanatory, the principal investigator trained those who administered the assessment in order to increase the reliability of the data. The training was quick, however, and was completed by telephone. This study was performed at 15 CALGB sites (ie, limited access study). This limited the accrual rate. In addition, the study population consisted of older adults who enrolled on cooperative group studies which could potentially limit the generalizability of the results; however, other studies utilizing this assessment tool in a broader population of older adults not enrolled on a clinical trial have demonstrated feasibility.[19,47] Lastly, few minority patients were included in this trial and black patients were more likely to decline participation. The under-representation of minority populations among older adults

Table 4. Study End Points

End Point	No. of Patients	%
Assessable patients	85	100
Patient completes the patient portion of the geriatric assessment tool without assistance	74	87
Health care provider completes the health care provider portion of the geriatric assessment tool	85	100
Patient report questionnaire length satisfactory	78	92
Patient reports no questions too difficult to understand	81	95
Patient reports no questions upsetting	82	96

Table 5. Geriatric Assessment Results

Domain With Measure	Mean	SD	Median	Range	Patients With Incomplete Data	
					No.	%
Functional status						
MOS physical health (scale 0 to 100)	82	16.8	85	15-100	4	5
Instrumental activities of daily living (scale 0 to 14)	13.8	0.7	14	9-14	0	0
Physician-rated Karnofsky performance status (scale 0 to 100)	94.8	8.2	100	60-100	2	2
Self-rated Karnofsky performance status (scale 40 to 100)	89.5	12.8	90	40-100	2	2
No. of falls in last 6 months	0.3	0.7	0	0-3	3	4
Timed Up and Go, seconds	12	6.6	10	6-56	1	1
MOS social activities (scale 0 to 100)	66	18.3	75	0-94	1	1
Comorbid medical conditions						
No. of comorbid medical conditions (physical health section [subscale of the OARS])	2.0	1.6	2	0-5	2	2
Psychological state						
Hospital Anxiety and Depression Scale (scale 0 to 42)	5.8	4.5	5	0-22	1	1
Social support						
MOS social support survey: emotional/information and tangible subscales	86	21.6	98	15-100	3	4
Nutritional status						
Body mass index	26.8	5.8	26	11-47	0	0
Percent weight loss in last 6 months	2.2	9.2	0	66% loss to 9% gain	7	8
Cognition						
Blessed Orientation-Memory-Concentration test (scale 0 to 28)	2.6	2.8	2	0-10	0	0
Medications						
No. of medications	5.6	3.4	5	0-20	0	0

NOTE. Report is based on 85 assessable patients.
Abbreviations: SD, standard deviation; MOS, Medical Outcomes Study; OARS, Older American Resources and Services.

enrolled on National Cancer Institute sponsored trials has been previously described.[48] Additional studies are needed to understand the rationale for this finding. In addition, further studies are needed to assess the feasibility of this geriatric assessment in minority populations.

Plans to further develop the geriatric assessment tool are under way. The Cancer and Aging Research Group[49] has accrued more than 600 older adults with cancer to a study evaluating the geriatric assessment tool's ability to predict the risk of toxicity to chemotherapy. The assessment has also been incorporated into a cooperative group study that evaluates hormone therapy with or without bevacizumab in postmenopausal patients with metastatic cancer. The assessment is captured at baseline and in longitudinal follow-up. Several other CALGB treatment studies under development are also incorporating this geriatric assessment. The feasibility of obtaining geriatric assessment information via touch-screen computer methodology is also under study. The next generation of studies will profit from results of this research to help guide interventions or to modify treatment plans in order to decrease the risk of toxicity while maintaining therapeutic efficacy in a growing population of older adults with cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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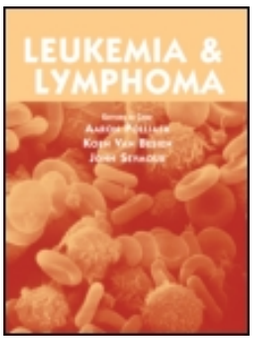

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Cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab versus epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab for the initial treatment of elderly "fit" patients with diffuse large B-cell lymphoma: results from the ANZINTER3 trial of the Intergruppo Italiano Linfomi

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Abstract

We conducted a prospective study to compare epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab (R-miniCEOP) with cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (R-CHOP) for the treatment of "fit" elderly patients with diffuse large B-cell lymphoma (DLBCL). Patients over the age of 65 with stage II–IV DLBCL were screened with a comprehensive geriatric assessment. Patients were randomized to receive six courses of R-miniCEOP ($n = 114$) or R-CHOP ($n = 110$). Overall, the rate of complete remission was 70% ($p = 0.466$). After a median follow-up of 42 months, 5-year event-free survival (EFS) rates were 46% and 48% for R-miniCEOP and R-CHOP, respectively ($p = 0.538$). Patients older than 72 years and with low-risk disease had a better outcome when treated with R-miniCEOP ($p = 0.011$). Overall R-CHOP and R-miniCEOP are similarly effective for elderly "fit" patients with DLBCL. The less intense R-miniCEOP may be an acceptable option for the treatment of relatively older patients with low-risk disease.

Keywords: R-CHOP, R-miniCEOP, diffuse large B-cell lymphoma, elderly, fit patients

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent subtype of non-Hodgkin lymphoma (NHL) and frequently affects elderly people [1]. For more than 20 years, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) has been the standard treatment for patients with aggressive NHL [2], with recent data supporting addition of the anti-CD20 monoclonal antibody rituximab (R-CHOP). The R-CHOP combination given every 3 weeks is the standard treatment for elderly patients with DLBCL and is associated with a 5-year overall survival (OS) rate of ~60% [3,4].

Management of elderly patients with lymphoma, however, is frequently a challenge for clinicians, mainly due to the presence of one or more co-morbid conditions and/or functional status impairments. Different strategies have been adopted to try to manage elderly patients better; these include the use of regimens with reduced doses of drugs, or less toxic drugs [5–8].

Fewer attempts have been made to try to prospectively identify patients who are eligible to receive full-dose treatment.

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There is an accompanying commentary that discusses this paper. Please refer to the issue Table of Contents.

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Although several tools are available to identify "fit" patients among the elderly population, published clinical trials usually leave the decision of whether or not to include a patient to the clinician's judgement.

In 2003 the Intergruppo Italiano Linfomi started a randomized trial to compare standard R-CHOP with a combination of rituximab and miniCEOP (epirubicin, cyclophosphamide, vinblastine and prednisone), a less intensive regimen specifically designed for elderly people and already tested by the same group [5]. In order to be registered and randomized, elderly patients with DLBCL had to be prospectively defined as "fit" according to comprehensive geriatric assessment (CGA) [9,10].

Table I. Drug doses and time schedules for R-CHOP and R-miniCEOP.

Drug	Dose (mg/m^2)	Route	Days
R-CHOP (every 21 days)			
Cyclophosphamide	750	IV	1
Doxorubicin	50	IV	1
Vincristine	1.4 (max. 2 mg)	IV	1
Prednisone	100 mg (fixed dose)	IV/PO	1–5
Rituximab	375	IV	1
R-miniCEOP (every 21 days)			
Cyclophosphamide	750	IV	1
Epirubicin	50	IV	1
Vinblastine	5	IV	1
Prednisone	50	IV/PO	1–5
Rituximab	375	IV	1

R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab; R-miniCEOP, epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab; IV, intravenously; PO, orally.

Materials and methods

The trial was conducted in compliance with the Declaration of Helsinki. It was also accepted by the appropriate Research Ethics Committees, and required each patient to give written informed consent prior to registration and randomization. The study was registered at the Clinicaltrial.gov website and assigned code NCT01148446.

Previously untreated patients older than 65 years of age, with a histologically confirmed diagnosis of DLBCL of follicular lymphoma grade IIIb, clinical Ann Arbor stage II, III or IV disease and Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, were eligible. Moreover, all patients were required to undergo a CGA that included evaluation of the following parameters: (1) activities of daily living (ADL), (2) co-morbidity score according to the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [11] and evaluated in all organs/systems as detailed by Balducci and Beghe [9]. Patients were classified in the category of "fit" if they had an ADL score of 6, less than three grade 3 CIRS-G co-morbidities and no grade 4 co-morbidities (hematological co-morbidities were not investigated), and none of the criteria defining the presence of geriatric syndrome. All other patients were classified as "unfit," and were excluded from randomization. Moreover, instrumental activities of daily living (IADL) were also tested for each patient (IADL score did not affect definition of patient status).

Eligible "fit" patients were randomly assigned to receive six courses of R-CHOP or R-miniCEOP. Patients with a less than partial response (PR) after the first three cycles of chemotherapy were removed from the study. R-CHOP was administered as originally reported [3]; the R-miniCEOP schedule is shown in Table I. Prophylactic granulocyte-colony stimulating factor (G-CSF) was recommended in cases of persisting grade 4 neutropenia or febrile neutropenia. All patients had to receive cotrimoxazole as anti-infectious prophylaxis. Erythropoietin use was allowed in cases of anemia (hemoglobin $<$11 g/dL) but was not mandatory.

At the end of chemotherapy, radiotherapy (RT) was scheduled for sites of previous bulky disease or partially responding sites.

Statistics and assessment of efficacy

All analyses were conducted according to the intention-to-treat (ITT) principle, with the provision that patients for whom an exclusion criterion was discovered after randomization would be considered ineligible. Baseline disease assessment was described with the Ann Arbor staging system; performance status was described on the five-point ECOG scale. Nodal sites were defined as bulky when larger than 10 cm if occurring outside the mediastinum; mediastinal masses were defined as bulky if their transverse diameter measured at the D5 level was larger than a third of the transverse diameter of the thorax at the same level, or if larger than 6 cm at computed tomography (CT) scan. For outcome assessment, the age-adjusted International Prognostic Index (aaIPI) was used as originally described [12].

The principal study endpoint was event-free survival (EFS), defined as the interval between the date of randomization and the occurrence of one the following events: lack of complete response, relapse, death from any cause, treatment interruption or treatment change, or late toxic events correlated to study treatment. Secondary endpoints were response rate (RR), overall survival (OS), relapse-free survival (RFS) and toxicity. OS was calculated for all patients from date of randomization to date of death, from whatever cause, or to date of last visit; tumor size and treatment response were estimated on the basis of international criteria [13].

Toxicity was measured and graded according to the standard ECOG criteria [14]; the toxicity of the two study regimens was analyzed, comparing the rate of grade III–IV events, and dose intensity (DI) was calculated according to Hryniuk [15].

All statistical analyses were accomplished using Stata Statistical Software, Release 8.2 (Stata Corp, College Station, TX). Survival curves were plotted using Kaplan–Meier estimates [16], and statistical comparisons between curves were made using the log-rank test. Comparisons between curves that had been adjusted by potential confounding factors (aaIPI, age, extranodal sites and bulky disease) were obtained using the Cox proportional hazards regression method [17]. The χ^2 test and Fisher exact test were used to compare variables when appropriate [18]. Effect modifier analysis was performed to assess lack of homogeneity of an arm effect across the levels of putatively influential factors [19]. Each factor was analyzed separately in dichotomous form, with continuous factors dichotomized according to the usual clinical thresholds, when possible, or at the median. The effect modifier analysis assessed the arm by factor interaction in a

statistical model that also included the arm and factor main effects. The evidence of effect modification was expressed using hazard ratio (HR) with 95% confidence interval (CI). Finally, a multivariate Cox proportional hazards (PH) regression was performed with a stepwise selection guide cut-off of 0.10. Proportionality of a hazard was graphically examined by means of the scaled Schoenfeld residuals [20]. Stability of the model was confirmed using 1000 bootstrap replications.

All statistical tests were two-sided. Sample size was calculated considering that the study was designed as a comparative two-arm randomized trial for testing the superiority of R-CHOP compared to R-miniCEOP, assuming EFS as the principal study endpoint, and assuming a 2-year EFS rate for R-miniCEOP of 40% and a 2-year EFS of 60% for R-CHOP. With a two-sided 5% significance test (α error = 0.05) and a power of 80% (β error = 0.2), 214 patients were enough to have 108 events, required to show a 44% risk reduction between arms. Taking into consideration a dropout rate of 5% after randomization, the sample size was defined at 226 patients (113 patients per arm). Enrollment was stopped in December 2006 when 228 patients from 37 centers had been enrolled and randomized.

Results

Between January 2003 and December 2006, 334 potentially eligible patients were referred to the study datacenter. Ninety-nine patients were considered as "unfit" at CGA and not randomized. Seven patients were subsequently excluded due to lack of data before randomization. Two hundred and twenty-eight patients were randomized, and four were excluded due to violation of inclusion criteria after randomization (diagnosis not allowed in two cases; concomitant prostate cancer in one; stage I disease in one). Among the remaining 224 patients, 110 and 114 were randomly allocated to R-CHOP and R-miniCEOP, respectively. Thus, 224 of the eligible subset of cases were analyzed according to intention-to-treat. A diagram of patient flow is reported in Fig. 1 and the baseline characteristics of our patients are shown in Table II.

Outcomes

At the end of treatment, the complete remission (CR) rate was similar in both arms: 73% (95% CI, 63–81%) and 68% (95% CI, 58–76%) for cases treated with R-CHOP and R-miniCEOP, respectively ($p = 0.466$). A summary of study results by treatment arm is shown in Table III. The median delivered DI was R-CHOP 0.92 (range 0.68–1.00) and R-miniCEOP 0.96 (range 0.77–1.10). A total of 35 patients received RT after chemotherapy (13 treated with R-CHOP and 22 with R-miniCEOP).

Overall, chemotherapy had to be discontinued in nine and 12 patients in the R-CHOP and R-miniCEOP arms, respectively. The main reason for treatment discontinuation was lack of response or disease progression in both arms (R-CHOP six cases, R-miniCEOP eight cases); other reasons for treatment discontinuation were one case each of infection, trauma and physician decision for R-CHOP, and two cases of cardiac dysfunction, and one case each of hematological toxicity and physician decision for R-miniCEOP. Thirteen patients out of 21 who discontinued the treatment died after the event. Another four patients died within 3 months from the end of treatment due to causes possibly related to treatment, resulting in a treatment related mortality (TRM) of 7.5%: 9.1% (10 patients) in the R-CHOP arm and 6.1% (seven patients) in the R-miniCEOP arm ($p = 0.457$).

After a median follow-up of 42 months for patients who were alive at the time of the last follow-up date ($n = 148$; range 5–81 months), 114 events had been recorded, including 69 responses less than CR, 34 relapses and 11 deaths in CR. Events occurred in 54 patients in the R-CHOP arm and in 60 patients in the R-miniCEOP arm. Overall, 76 patients died: 38 in the R-CHOP arm and 38 in the R-miniCEOP arm. Of these, 43 patients died as a result of lymphoma

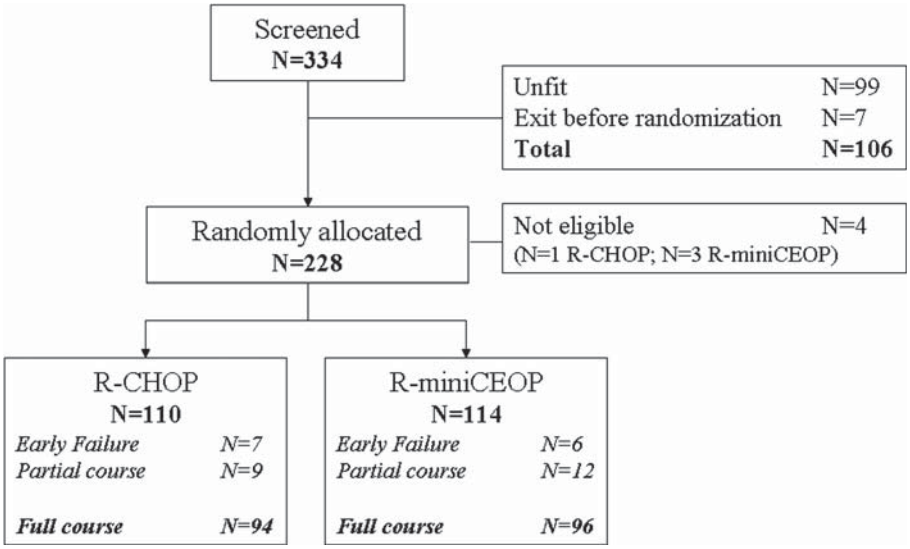

Figure 1. Treatment allocation and number of patients included in the analysis, according to the CONSORT statement. Note: After 334 patients had been screened, 99 patients were considered "unfit" for randomized trial and seven patients were excluded before the randomization. After randomization four patients were considered ineligible and were excluded. Patients were included in the analysis according to the intention-to-treat principle. Thirty-four patients did not receive all six scheduled cycles of chemotherapy (16 patients in R-CHOP and 18 patients in R-miniCEOP).

Table II. Patients' characteristics in the two treatment arms.

		R-CHOP (n = 110)		R-miniCEOP (n = 114)		Total (n = 224)		
		n	%	n	%	n	%	p-Value†
Gender	F	55	50	65	57	120	54	0.348
	M	55	50	49	43	104	46	
Age median (range)		71 (65–86)		73 (64–84)		72 (65–86)		0.341
Age	>72	43	39	58	51	101	45	0.082
AA stage	II	37	34	33	29	70	31	0.474
	III–IV	73	66	81	71	154	69	
PS	0–1	100	91	96	84	196	88	0.158
	2+	10	9	18	16	28	12	
LDH*	NV	44	41	47	44	91	42	0.678
	>1 UNL	64	59	59	56	123	58	
B2M*	NV	27	34	22	26	49	30	0.393
	>1 UNL	53	66	61	74	114	70	
Bulky*	−	79	72	90	79	169	76	0.277
	+	30	28	24	21	54	24	
ENS*	0–1	81	75	79	69	160	72	0.372
	>1	27	25	35	31	35	28	
Symptoms	A	67	61	68	60	135	60	0.892
	B	43	39	46	40	89	40	
aaIPI*	0	20	18	14	13	34	16	0.117
	1	36	33	44	42	80	37	
	2	46	43	35	33	81	38	
	3	6	6	13	12	19	9	
IADL	Score <8	26	24	22	19	48	21	0.327
CIRS-G	Score 1–2	97	88	98	86	195	87	0.693
	Score 3	13	12	16	14	29	13	

R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab; R-miniCEOP, epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab; AA, Ann Arbor; PS, performance status; LDH, lactate dehydrogenase; B2M, β_2-microglobulin; ENS, number of extranodal sites; aaIPI, age-adjusted International Prognostic Index; IADL, instrumental activities of daily living; CIRS-G: Cumulative Illness Rating Scale for Geriatrics; NV, normal value; UNL, upper normal limit.
*Missing data: LDH (n = 10), B2M (n = 61), bulky (n = 1), ENS (n = 2), aaIPI (n = 10).
†p-Value: from Fisher's exact test, except Mann–Whitney test for age in continuous form.

progression or recurrence; other causes of death were recorded as complications/toxicity of first-line treatment in 17 patients, myocardial infarction during follow-up in four, second cancer in four, complications of salvage treatment in two, sudden death in two and one patient each due to stroke and car accident. In two cases, the cause of death was not known. Comparing R-CHOP and R-miniCEOP, causes of death were equally distributed between study arms, with the exception of a trend toward a higher number of deaths for lymphoma relapse/progression in the R-miniCEOP group (47% vs. 66% of all deaths, respectively; $p = 0.165$).

Table III. Summary of study results by treatment arm.

		R-CHOP (n = 110)		R-miniCEOP (n = 114)		
Response	%	n		n	%	p-Value
CR		80	73	77	68	0.466
PR		15	14	15	13	—
ORR		95	87	92	81	0.284
SD/PD		8	8	16	14	—
E-W		7	7	6	5	—
Survival (%)						
5-year OS		62 (51–71)		63 (52–72)		0.702
5-year EFS		48 (37–58)		46 (36–55)		0.538
Toxicity* (grade III–IV)						
Anemia		8	9	5	5	0.392
Neutropenia		20	23	22	23	1.000
Thrombocytopenia		2	2	2	2	1.000
Infections		7	8	2	2	0.090
Arrhythmia		0	0	1	1	1.000
Nausea/vomiting		3	3	1	1	0.348

R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab; R-miniCEOP, epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab; CR, complete remission; PR, partial response; ORR, overall response rate; SD, stable disease; PD, progressive disease; E-W, early withdrawal; OS, overall survival; EFS, event-free survival.
*Toxicity data were available in 185 patients.

With respect to initial study design and hypothesis, 2-year EFS was 55% (49–62%), being 57% and 54% in the R-CHOP and R-miniCEOP arms, respectively (two-sided χ^2 test; $p = 0.678$).

Overall the estimated 5-year EFS was 47% (95% CI: 40–54%): 48% (95% CI: 37–58%) and 46% (95% CI: 36–55%) for R-CHOP and R-miniCEOP, respectively ($p = 0.538$); the 5-year OS for the whole series was 62% (95% CI: 55–69%): 62% (95% CI: 50–71%) and 63% (95% CI: 52–72%) for R-CHOP and R-miniCEOP, respectively ($p = 0.702$) (Fig. 2).

We performed univariate analysis for EFS and OS considering aaIPI risk groups, age, bulky disease and number of extranodal sites (ENS) as covariates. Age with a cut-off at 72 years and aaIPI (0–1 vs. 2–3 risk factors) were significant predictors for EFS with the addition of bulky disease, and were the only prognostic factors for OS (data not shown). In multivariate analysis aaIPI was confirmed to be an independent prognostic factor both for EFS and for OS; age above 72 years was an independent prognostic factor for OS and borderline for EFS (Table IV). Regarding EFS, the hazard ratio calculated with proportional hazards regression analysis between R-miniCEOP and R-CHOP was 1.12 (95% CI: 0.78–1.6), with a log-rank p-value of 0.538. This result was not modified by any of the potential effect modifiers. When the analysis was performed for OS the R-miniCEOP showed a better performance compared to R-CHOP in the age group older than 72 years (Fig. 3). Thus, we created four groups and performed an OS analysis: age <72 with aaIPI 0–1 (n = 64, 30%) or aaIPI 2–3 (n = 55, 26%), and age >72 with aaIPI 0–1 (n = 50, 23%) or aaIPI 2–3 (n = 45, 21%). According to this analysis, patients with age > 72 years and low aaIPI (0–1) had a better outcome when treated with R-miniCEOP compared to those

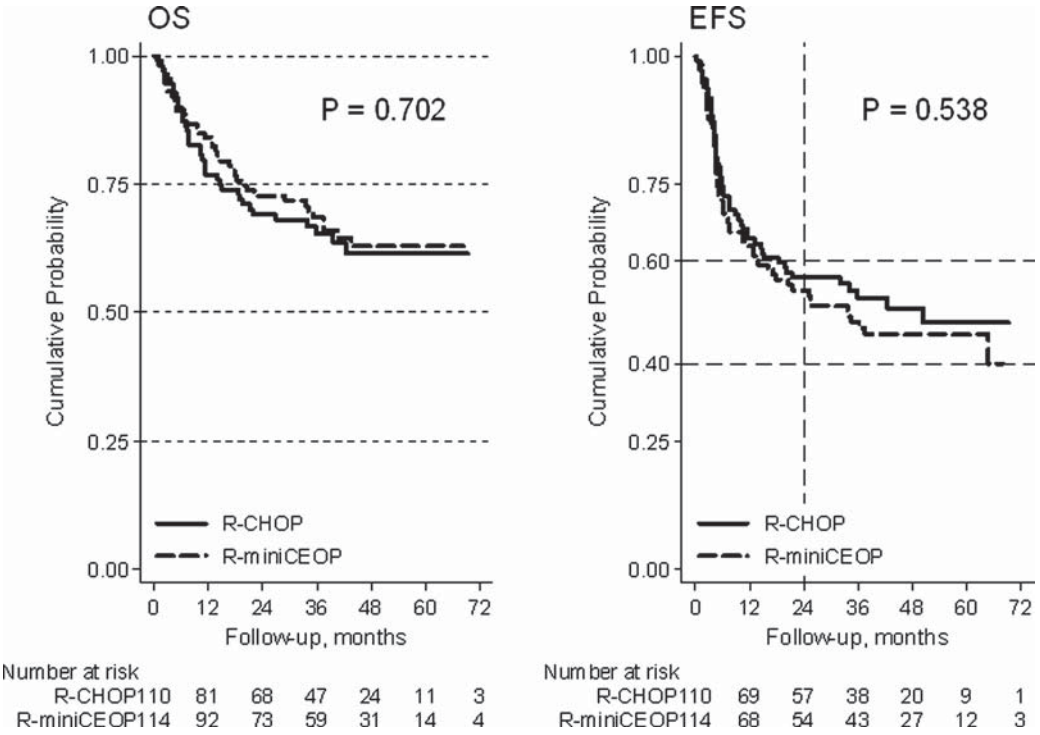

Figure 2. Overall survival (OS) and event-free survival (EFS) stratified by intention-to-treat approach. Crossing dashed lines in EFS correspond to probability at 2 years originally assumed in the trial.

treated with R-CHOP (HR = 0.13, $p = 0.011$) (Fig. 4). Also in EFS, treated patients with age > 72 and low aaIPI had a better outcome: HR 0.36 (95% CI 0.14–0.95), $p = 0.040$.

Results of comprehensive geriatric assessment

All randomized patients were defined as "fit" at CGA according to the protocol inclusion criteria. A detailed report of the CGA results is shown in Table II. Interestingly, single IADL or co-morbidity scores did not allow us to further identify prognostic subgroups in terms of EFS or OS, among randomized "fit" patients (data not shown).

Toxicity

A summary of the most common toxic events is shown in Table III. The most frequent event was neutropenia, without differences in the rate of grade III–IV events between the two arms (23%). A trend toward a higher rate of severe infections was observed in patients treated with R-CHOP (8%) compared with those treated with R-miniCEOP (2%) ($p = 0.090$). Overall four patients had a diagnosis of second cancer, including one acute myeloid leukemia (M5) at month 30, one bladder carcinoma diagnosed at month 36 and one pancreatic cancer diagnosed after 16 months, among patients randomized to R-CHOP, and one peritoneal carcinoma diagnosed after 34 months in a patient assigned to R-miniCEOP.

Table IV. Estimates of hazard ratio from multivariate Cox proportional hazards regression for EFS and OS.

		Univariate			Multivariate		
Factor		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
EFS							
Age	>72	1.38	0.95–2.00	0.088	1.44	0.98–2.10	0.061
aaIPI	2–3	3.13	2.09–4.69	<0.001	3.19	2.12–4.78	<0.001
Bulky	+	1.57	1.05–2.36	0.029			
ENS	>1	1.45	0.98–2.15	0.063			
OS							
Age	>72	1.58	1.02–2.48	0.046	1.79	1.12–2.85	0.014
aaIPI	2–3	3.99	2.36–6.75	<0.001	4.15	2.45–7.03	<0.001
Bulky	+	1.58	0.97–2.58	0.067			
ENS	>1	1.40	0.87–2.26	0.165			

EFS, event-free survival; OS, overall survival; aaIPI, age-adjusted International Prognostic Index; ENS, number of extranodal sites; HR, hazard ratio; CI, confidence interval.

Discussion

This randomized trial was designed to compare the efficacy of standard R-CHOP with a less intense regimen (R-miniCEOP) for the treatment of elderly patients with DLBCL prospectively defined as "fit" at CGA assessment. Based on our results, six courses of R-miniCEOP administered every 21 days are similarly effective to six courses of R-CHOP for the initial treatment of elderly "fit" patients with DLBCL. These results compare favorably with those achieved in other trials for the initial treatment of elderly patients with DLBCL. In particular, both the CR rate and OS achieved in our trial are comparable with those achieved in the R-CHOP arm of the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trial (CR 76%; 5-year EFS 47%; 5- and 10-year OS 58% and 44%) [4,22], and in the R-CHOP arm of the intergroup US trial (CR/PR 77%; 3-year FFS 52%; 3-year OS 67%) [23]. Higher rates of CR (78%), 3-year EFS (66.5%) and OS (78.1%) could be achieved with six courses of the more intense R-CHOP14 arm of RICOVER-60, although some concerns on the feasibility of such an intense approach remain [24]. A recent study of the HAEMACARE project [25] showed that the estimated

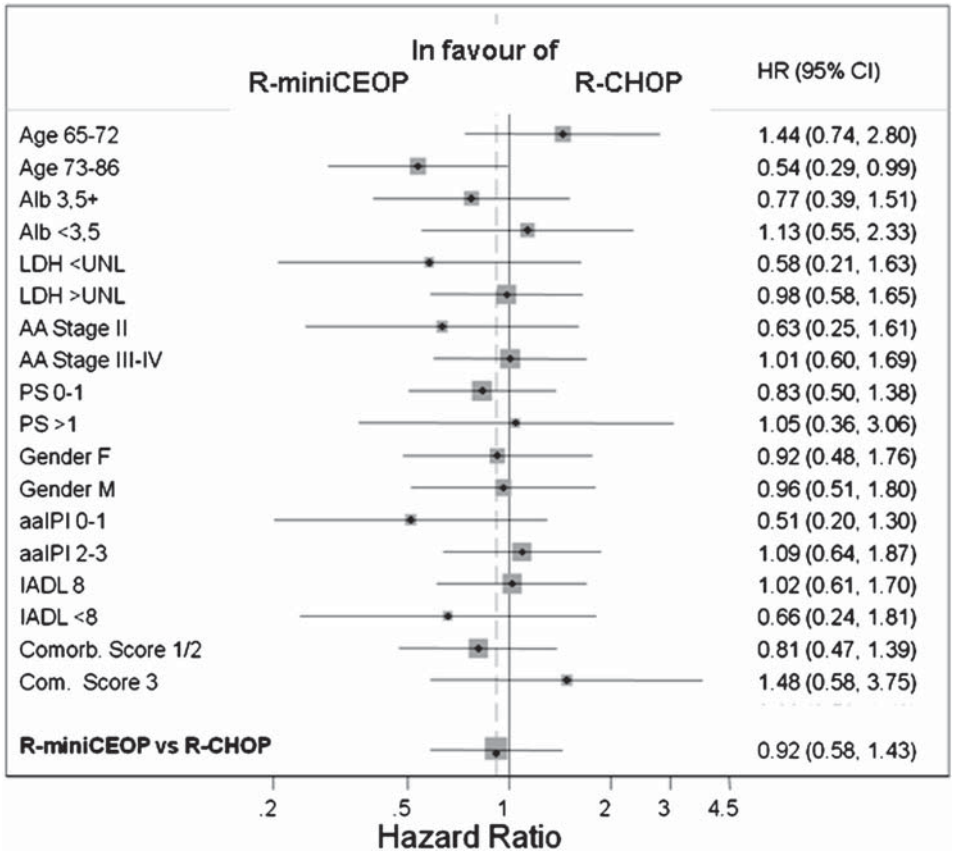

Figure 3. Effect modifier analysis. Forest plot for potentially confounding factors for overall survival (OS). Note: Continuous covariates age, erythrocyte sedimentation rate (ESR) and platelets were dichotomized at the median. Dashed vertical line: HR = 0.92, unadjusted comparison between R-miniCEOP and R-CHOP. Co-morbidity score: 1/2 fair, 3 moderate. Alb, albumin; LDH, lactate dehydrogenase; AA, Ann Arbor; PS, performance status; aaIPI, age-adjusted International Prognostic Index; IADL, instrumental activities of daily living.

relative survival in DLBCL in Europe (cohort of diagnosis 2000–2002) was 34.9%, after 5 years from diagnosis, in the age range 70–99.

Our study, showing a relative survival of 72% at 5 years, along with results of the other trials, highlights that there is a wide gap between the clinical trials and daily clinical practice.

Several trials investigated the role of regimens specifically designed for elderly patients with aggressive lymphoma and compared them with CHOP or CHOP-like chemotherapy in randomized trials [26–28]. All these studies demonstrated that less intense regimens achieved poorer results; however, no similar comparison has been performed in the era of chemoimmunotherapy. To our knowledge this is the first trial that was designed to assess the efficacy of a regimen less intense than CHOP and that also includes rituximab. Although it is difficult to estimate the differences in terms of dose intensity between study regimens, by applying the summation dose intensity (SDI) method proposed by Hryniuk *et al*. for comparing dose intensity of different chemotherapy regimens in advanced breast cancer [29] we can assume that miniCEOP has 30% reduction of SDI compared with CHOP. The absence of significant differences between the two study arms thus suggests that the anti-CD20 monoclonal antibody used may have acted as a treatment equalizer.

No statistically significant differences in toxicity between the two arms were observed. The main event was represented by neutropenia (23%), with lower rates compared to other studies, which can be partly explained by the prophylactic use of G-CSF. Overall the rate of treatment-related deaths was 7.6%, which may appear unexpectedly elevated, but this is still comparable to that described for the GELA trial (6%) [3] and for the US intergroup study (5%) [23]. Most deaths occurred during treatment; however, 25% of such events occurred within 3 months from the end of treatment, confirming the hypothesis that elderly patients undergoing chemotherapy may show a prolonged risk of treatment-related toxicity. Finally, 7% of patients (21% of all deaths) died during follow-up due to causes not related to lymphoma; again, no differences between the study arms were observed: myocardial infarction and second cancer were the most frequently registered causes of death, with four cases each (5% of all deaths).

One of the most relevant findings of our study is that for relatively older patients (older than 72 years) with low-risk disease (aaIPI 0–1) the less intense R-miniCEOP may be a better choice than standard R-CHOP. The trial was not powered to identify small differences of study endpoints between study arms, but our hypothesis is that R-CHOP, even if it is tolerable in elderly people, may become detrimental in relatively "frailer" patients with less aggressive disease. Looking at the study results, patients treated with R-CHOP had a trend toward a better response rate and a reduced risk of death due to lymphoma relapse or progression that was

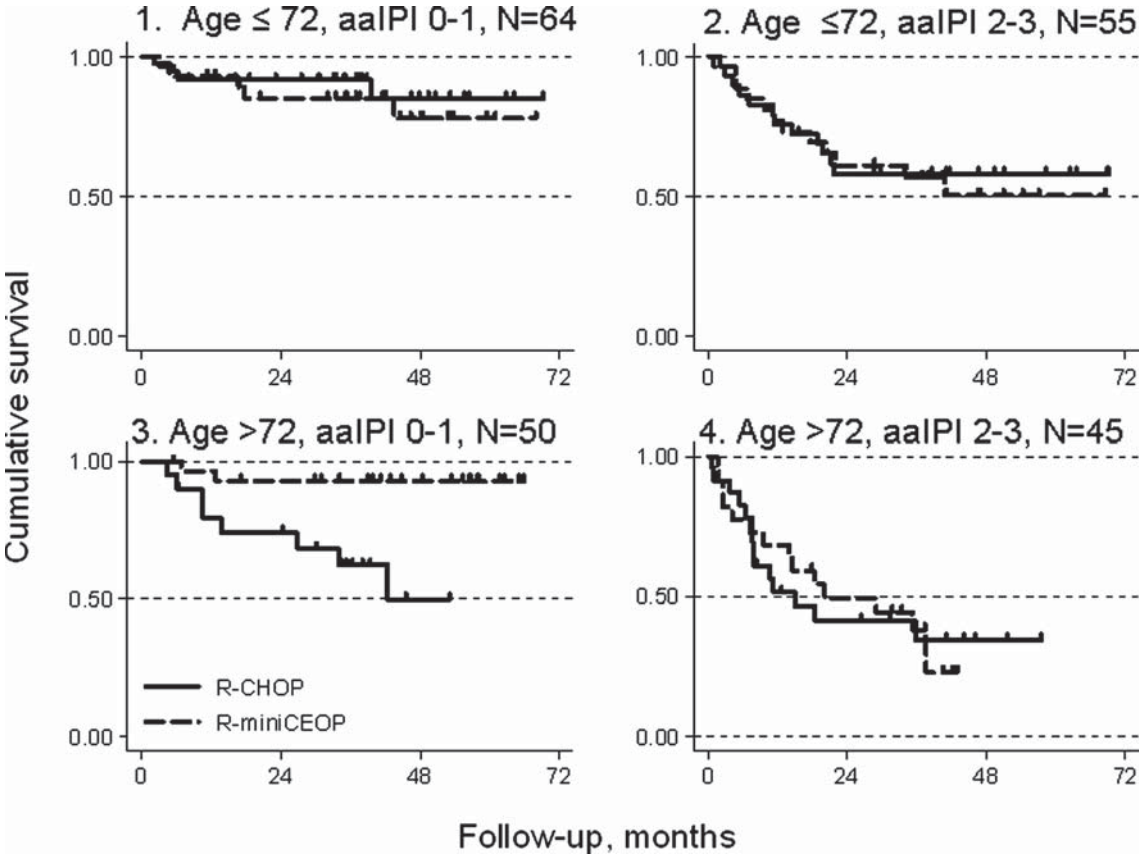

Figure 4. Overall survival estimated with Kaplan–Meier method stratified by age and aaIPI. Comparison R-miniCEOP (dashed line) vs. R-CHOP (solid line). 1. HR = 1.57, $p = 0.501$; 2. HR = 1.11, $p = 0.803$; 3. HR = 0.13, $p = 0.011$; 4. HR = 1.04, $p = 0.923$.

counterbalanced by a non-statistically significant increase in the rate of severe infections and of treatment-related deaths. For very old patients with low-risk disease, less intense regimens such as R-miniCEOP may then be a better strategy, as they are more focused on preserving the patient from unnecessary toxicity, compared with R-CHOP. The use of age as a prognostic variable to further discriminate elderly patients at different risk of failure or death has been recently confirmed by Advani *et al.* [30]; however, additional trials specifically powered to verify our hypothesis are warranted.

Prospective assessment of patient "status" was one of the most important features of this study, and was introduced to avoid subjective evaluation of a patient's ability to receive full-dose therapy. Currently used criteria for registering patients are usually limited to the assessment of performance status and/or to non-validated criteria generally referred to as: "in the opinion of the investigator the general status of the patient did permit the administration of 8 courses of CHOP" [3]; or "if patient is able to comply with study requirements" [24]. In our study unfit patients had an HR of 3.03 (95% CI, 2.17–4.23) compared to fit patients for the risk of death, and showed a poorer outcome also if treated with a rituximab-containing regimen (HR 2.34; 95% CI, 1.43–3.83) [23]. These data support the use of CGA as a good tool to select "fit" patients, confirming previous reports [10,31]. Indeed, the adoption of such an approach makes our results more reproducible, as patient selection was not left to subjective assessment. Moreover, even though the present trial was not designed to verify the effectiveness of CGA to identify patients who can receive full-dose treatment, considering the elevated median age and the inclusion of very old patients in our trial, we hypothesize that this is the result of a better selection of patients. CGA is then a tool that extends the possibility of adopting full-dose chemotherapy in elderly patients with DLBCL and ultimately improving curability. Further improvement in the approach to elderly patients undergoing systemic chemotherapy may be achieved in future studies by investigating patients' functionality and quality of life during treatment and follow-up.

In conclusion, based on our results, we confirm that a good proportion of elderly patients with DLBCL can be cured with immunochemotherapy. The choice of the optimal therapy for each individual patient should be based on an accurate assessment of disease risk and of the patient's status through the adoption of validated tools to identify "fit" patients, such as CGA. Finally, our results also suggest that availability of the anti-CD20 monoclonal antibody can allow the use of less-intense chemotherapy regimens such as mini-CEOP, and that this can an acceptable option for the treatment of relatively older patients with low-risk disease.

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Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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ORIGINAL REPORT

Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC-GECP 08-02 Study

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See accompanying article on page 1438

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Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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ABSTRACT

Purpose

Comprehensive geriatric assessment (CGA) is recommended to assess the vulnerability of elderly patients, but its integration in cancer treatment decision making has never been prospectively evaluated. Here, in elderly patients with advanced non–small-cell lung cancer (NSCLC), we compared a standard strategy of chemotherapy allocation on the basis of performance status (PS) and age with an experimental strategy on the basis of CGA.

Patients and Methods

In a multicenter, open-label, phase III trial, elderly patients ≥ 70 years old with a PS of 0 to 2 and stage IV NSCLC were randomly assigned between chemotherapy allocation on the basis of PS and age (standard arm: carboplatin-based doublet if PS ≤ 1 and age ≤ 75 years; docetaxel if PS = 2 or age > 75 years) and treatment allocation on the basis of CGA (CGA arm: carboplatin-based doublet for fit patients, docetaxel for vulnerable patients, and best supportive care for frail patients). The primary end point was treatment failure free survival (TFFS). Secondary end points were overall survival (OS), progression-free survival, tolerability, and quality of life.

Results

Four hundred ninety-four patients were randomly assigned (standard arm, n = 251; CGA arm, n = 243). Median age was 77 years. In the standard and CGA arms, 35.1% and 45.7% of patients received a carboplatin-based doublet, 64.9% and 31.3% received docetaxel, and 0% and 23.0% received best supportive care, respectively. In the standard and CGA arms, median TFFS times were 3.2 and 3.1 months, respectively (hazard ratio, 0.91; 95% CI, 0.76 to 1.1), and median OS times were 6.4 and 6.1 months, respectively (hazard ratio, 0.92; 95% CI, 0.79 to 1.1). Patients in the CGA arm, compared with standard arm patients, experienced significantly less all grade toxicity (85.6% *v* 93.4%, respectively $P = .015$) and fewer treatment failures as a result of toxicity (4.8% *v* 11.8%, respectively; $P = .007$).

Conclusion

In elderly patients with advanced NSCLC, treatment allocation on the basis of CGA failed to improve the TFFS or OS but slightly reduced treatment toxicity.

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INTRODUCTION

Lung cancer is the most common malignancy worldwide and the leading cause of cancer-related deaths in Western countries.[1] Approximately 50% of patients with non–small-cell lung cancer (NSCLC) are 70 years of age or older at diagnosis.[2] Concerning advanced NSCLC, international treatment guidelines have evolved significantly over the past 15 years.[3,4] In 2004, the American Society of Clinical Oncology guidelines recommended single-agent chemotherapy.[5] Guidelines published in 2009 considered there was no evidence to support the use of a particular first-line drug or combination on the basis of age alone and that both physiologic age and performance status

(PS) should be taken into account.[6] At that time, subgroup analyses of clinical trials of platinum-based doublets in patients unselected for age suggested that carefully selected elderly patients could receive this treatment.[7,8] In 2011, a phase III trial in fit elderly patients demonstrated the superiority of a monthly carboplatin and weekly paclitaxel doublet over vinorelbine or gemcitabine monotherapy in terms of overall survival (OS).[9] Consequently, current guidelines recommend first-line treatment with a carboplatin-based doublet for fit elderly patients and consider that single-agent treatment is an option for less fit patients; no specific recommendations are made for octogenarians.[10] However, there is no consensus definition of fit or less fit patients. In clinical practice, elderly patients form a heterogeneous population with baseline organ dysfunctions and with variable numbers of comorbidities correlating poorly with functional status.[11] These patients are often taking several medications and may also have a geriatric syndrome and suffer from social isolation, including poor caregiver support. This makes it difficult for clinicians to follow these recommendations.

Comprehensive geriatric assessment (CGA) is based on a multidisciplinary and global approach to elderly patients, covering functional status, cognitive capacities, emotional status, comorbidities, nutritional status, polypharmacy, social and environmental situations, and a possible geriatric syndrome. CGA can predict morbidity and mortality in elderly patients with cancer[11] and can help to adapt cancer management to each patient's fitness or frailty.[12] Balducci and Extermann[13] used a practical CGA-based approach to define the following three therapeutic groups of elderly patients: standard therapy for fit patients, adjusted therapy for vulnerable patients, and best supportive care (BSC) for frail patients. Our group (Groupe Français de Pneumo-Cancérologie) showed in phase II studies that CGA can identify homogenous groups of fit and frail patients.[14-17] However, even if the use of CGA is encouraged in several guidelines,[10,18] there is no firm evidence of its feasibility or utility in routine clinical practice.[19]

We conducted a multicenter, randomized, phase III trial in elderly patients (≥ 70 years) with stage IV NSCLC, comparing a standard strategy of treatment allocation (carboplatin-based doublet or single agent on the basis of PS and age) with experimental CGA-based allocation of the same chemotherapies or BSC. In both arms, the associated drug included in the carboplatin doublet was based on histologic findings. Single-agent therapy consisted of weekly docetaxel because previous studies have demonstrated its efficacy and favorable safety profile.[14,20,21]

PATIENTS AND METHODS

Patients

The main eligibility criteria were age ≥ 70 years, histologically or cytologically proven advanced NSCLC, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0, and Eastern Cooperative Oncology Group PS of 0 to 2. Adequate hematologic, renal (creatinine clearance ≥ 45 mL/min using Modification of Diet in Renal Disease equation), and hepatic function was required. At inclusion, *EGFR* and *ALK* status was wild type or unknown. The main exclusion criteria were severe concurrent disorders, active malignancy within the past 5 years, and symptomatic brain metastases. Patients with a bronchoalveolar, neuroendocrine, or composite cancer histology were not eligible. All enrolled patients gave their written informed consent. The study was approved by the Rennes Ethics Committee and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

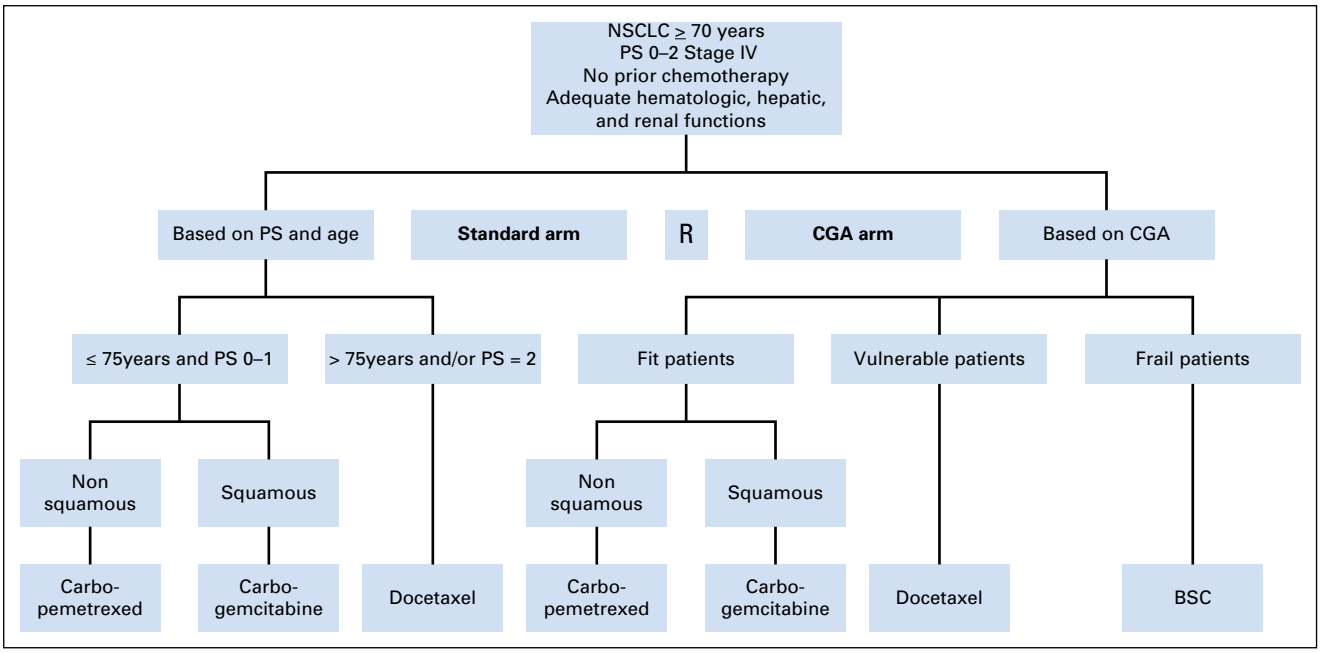

Fig 1. Study design and chemotherapy schedules. Four cycles of chemotherapy were to be administered every 3 weeks; chemotherapy involved a carboplatin (Carbo)–based doublet (for nonsquamous histology: Carbo [area under the curve 5 on day 1] plus pemetrexed [500 mg/m^2 on day 1]; for squamous histology: Carbo [area under the curve 5 on day 1] plus gemcitabine [1,000 mg/m^2 on days 1 to 8]) or single-agent treatment (docetaxel 38 mg/m^2 on days 1 to 8). BSC, best supportive care; CGA, comprehensive geriatric assessment; NSCLC, non–small-cell lung cancer; PS, performance status; R, random assignment.

Table 1. Definition of Fit, Vulnerable, and Frail Patients in the CGA Arm

Geriatric Parameters	Fit: All Criteria	Vulnerable: One of the Bold Criteria	Frail: One of the Bold Criteria
PS	0 or 1	**2**	0-2
ADL (0-6)	6	6	**≤ 5**
IADL (0-4)	0	**1**	**≥ 2**
Schultz-Larsen MMSE (0-11)	≥ 9		
Folstein MMSE (0-30)		> 23	**≤ 23**
Geriatric syndrome	No	No	**Yes**
Charlson comorbidity index	0-1	**2-3**	**≥4 (≥ 3 if > 80 years)**
GDS5 (0-5)	0-1	**2-3**	**4-5**

NOTE. Patients were considered fit if they met all the following criteria that constitute an abbreviated geriatric assessment: PS of 0-1, ADL score of 6, IADL score of 0, Schultz-Larsen MMSE ≥ 9, no geriatric syndrome (confirmed dementia, repeated falls, or urinary or fecal incontinence), Charlson comorbidity index ≤ 1, GDS5 score of 0 to 1. If patients were not fit, the Folstein MMSE was also considered. Patients were considered vulnerable if they met one or more of the following criteria: PS of 2, IADL score of 1, Charlson comorbidity index of 2 to 3, or GDS5 score of 2 to 3. Patients were considered frail if they met one or more of the following criteria: ADL score ≤ 5, IADL score ≥ 2, Folstein MMSE ≤ 23, presence of geriatric syndrome (confirmed dementia, repeated falls, or urinary or fecal incontinence), Charlson comorbidity index ≥ 4 (or ≥ 3 if > 80 years), or GDS5 of 4 to 5.

Abbreviations: ADL, activities of daily living; CGA, comprehensive geriatric assessment; GDS5, Geriatric Depression Scale 5; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; PS, performance status.

Study Design

All patients had a CGA performed by their regular cancer physician. The domains explored and the scales used are described in Appendix Table A1 (online only). The protocol included no specific interventions to improve problems detected by the CGA. The patients were stratified by center and randomly assigned at a 1:1 ratio to the two arms (Fig 1). In the standard arm, patients with PS ≤ 1 and age ≤ 75 years received a carboplatin-based doublet according to their tumor histology, namely carboplatin (area under the curve 5 on day 1) plus pemetrexed (500 mg/m^2 on day 1) for nonsquamous carcinoma and carboplatin (area under the curve 5 on day 1) plus gemcitabine (1,000 mg/m^2 on days 1 to 8) for squamous carcinoma. Patients with a PS of 2 and/or age greater than 75 years received single-agent docetaxel (38 mg/m^2 on days 1 to 8). In the CGA arm, the following three groups of patients were defined according to the CGA (Table 1): fit patients received the same histology-based carboplatin doublet as in the standard arm; vulnerable patients received single-agent docetaxel; and frail patients received BSC (Fig 1). The maximum allowed delay between random assignment and initiation of treatment was 10 days. In both arms, four cycles of chemotherapy every 3 weeks were planned for patients receiving chemotherapy; maintenance therapy was not offered. Growth factor support was not recommended as primary prophylaxis but was authorized as secondary prophylaxis.

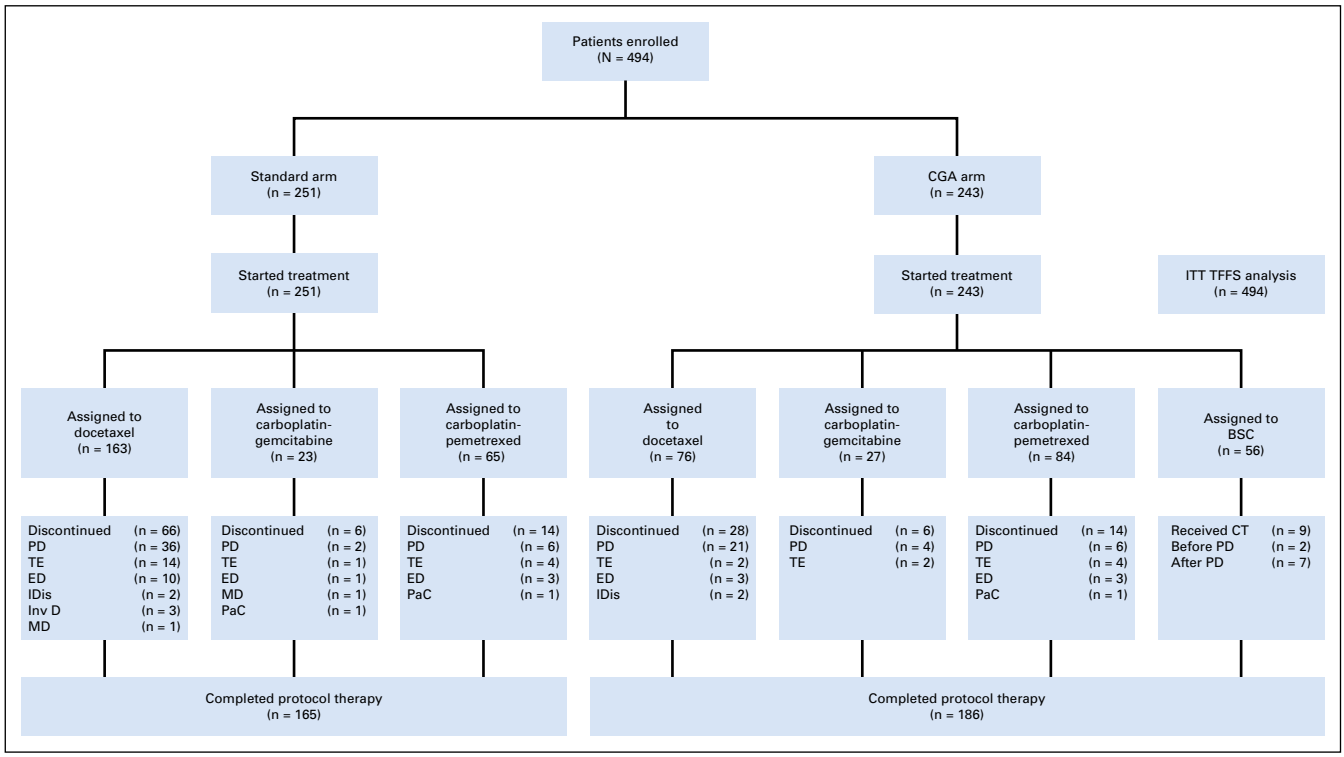

Fig 2. CONSORT diagram showing patient registration, treatment arm assignments, and reasons for discontinuation. Discontinued indicates patients who did not receive the four planned cycles. BSC, best supportive care; CT, chemotherapy; ED, early death; IDis, intercurrent disease; InvD, investigator's decision; ITT, intention to treat; MD, missing data; PaC, patient's choice; PD, progressive disease; TE, toxic effect; TFFS, treatment failure–free survival.

Outcome Measures

The primary end point was the treatment failure–free survival (TFFS), which was defined as the time elapsing between random assignment and early treatment discontinuation as a result of any reason (including disease progression, treatment toxicity, or early death), disease progression, or death (resulting from any cause). Secondary end points included OS, progression-free survival (PFS; defined as the time from random assignment to progression or death), overall response rate, tolerability, quality of life (QoL), and QoL-adjusted survival. The tumor response was assessed by computed tomography 6 and 12 weeks after random assignment and then every 8 weeks until disease progression, trial exit for toxicity, death, or withdrawal of consent. Disease progression was assessed by a panel of investigators blinded to the group allocation, independently of the treating investigator. Adverse events (Aes) and serious Aes were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Symptoms and QoL were evaluated from random assignment to each tumor assessment using the Lung Cancer Symptom Scale and the EuroQol EQ-5D questionnaires.

Statistical Analysis

This study was designed to detect a 30% improvement in TFFS, with an assumed median TFFS time of 3.4 months in the standard arm and 4.5 months in the CGA arm, with a statistical power of 80%, a two-sided type I error of 5%, and a 5% rate of loss to follow-up. This required 490 patients to be enrolled over 3 years with a minimum follow-up of 12 months. Efficacy analyses were performed on an intent-to-treat basis. TFFS, OS, and PFS were analyzed using Cox proportional hazards regression models and are reported as Kaplan-Meier estimates with hazard ratios and 95% CIs. Differences between the arms were assessed using a two-sided log-rank test. Subgroup analyses of TFFS were performed using baseline characteristics (sex, age, and PS) and geriatric characteristics (eg, Mini-Mental State Examination and activities of daily living [ADL] scores) as stratification variables. To identify factors potentially influencing TFFS, a multivariate Cox model was constructed with stepwise variable selection. We used univariate Cox models to select baseline variables ($P = .20$) for the multivariate analysis. Given the longitudinal nature of the QoL data, a linear mixed-effects model was used to compare the utility score and, therefore, QoL between the standard and CGA arms. Finally, QoL-adjusted survival was estimated, and the average QoL-adjusted survival time was compared between the arms.[22,23] Usual statistical tests (χ^2 test, Fisher's exact test, and Wilcoxon Mann-Whitney U test) were used to compare variables between the arms. A value of $P < .05$ was considered statistically significant. Data were analyzed using SAS software 9.3 (SAS Institute, Cary, NC). The trial is registered with ClinicalTrials.gov (identifier: NCT 01257139).

RESULTS

Between January 2010 and January 2013, 494 patients were enrolled by 45 centers in France and Spain (14 university hospitals, four cancer centers, and 27 community hospitals), and 251 and 243 patients were assigned to the standard and CGA arms, respectively (Fig 2). Median age was 77 years. Baseline characteristics (Table 2) were well balanced, except that more patients in the CGA arm than the standard arm had an ADL score of 6 (89.3% *v* 82.1%, respectively). Median follow-up was 4.5 months (range, 0 to 36.7 months), and the final cutoff date was March 2014. Median time spent on CGA administration was 35 minutes. In the standard arm, 35.1% of patients received a carboplatin doublet and 64.9% received docetaxel. In the CGA arm, 45.7%, 31.3%, and 23.0% of patients received a carboplatin doublet, single-agent therapy, and BSC, respectively (Table 3). The median number of treatment cycles was four (range, one to four cycles) in both arms after excluding patients assigned to BSC in the CGA arm.

There was no significant difference between the arms with respect to TFFS time (3.2 *v* 3.1 months in the standard and CGA arms, respectively; hazard ratio, 0.91; 95% CI, 0.76 to 1.1; $P = .32$). In the standard arm, the median TFFS times among patients treated with a carboplatin doublet and with docetaxel were 4.4 and 2.9 months, respectively (Fig 3). In the CGA arm, the median TFFS times among patients treated with a carboplatin doublet, single-agent docetaxel, and BSC were 4.8, 2.6, and 1.3 months, respectively (Table 3). The reasons for treatment failure (Table 3) were not significantly different between the arms, except that failures as a result of toxicity were more frequent in the standard arm than the CGA arm (11.8% *v* 4.8%, respectively; $P = .007$). This difference persisted when patients managed with BSC in the CGA arm were excluded, but it was no longer statistically significant (11.8% *v* 6.3% in the standard and CGA arms, respectively; $P = .06$).

PFS did not differ significantly between the standard and CGA arms (3.7 *v* 3.4 months, respectively; $P = .59$; Appendix Fig A1, online only). After progression, 40.6% and 41.1% of patients in the standard and CGA arms, respectively, received a further line of treatment (more frequently after doublet therapy in both arms; Appendix Table A2, online only), and 17.6% of the patients managed exclusively with BSC received a systemic treatment after progression. OS was not significantly different between the standard and CGA arms (6.4 *v* 6.1 months, respectively; $P = .87$; Appendix Fig A2, online only). In the standard arm, median OS times among patients treated with a carboplatin doublet and with docetaxel were 8.6 and 5.7 months, respectively. In the CGA arm, median OS times among patients treated with a carboplatin doublet, single-agent docetaxel, and BSC were 10.0, 4.9, and

Table 2. Baseline Patient Characteristics

Characteristic	Standard Arm (n = 251)	CGA Arm (n = 243)
Age, years		
Median	76	77
Range	70-91	70-87
Men, %	74.5	74.1
Histology, %		
Squamous	27.1	28.8
Nonsquamous	72.9	71.2
Never-smokers, %	20.8	19.6
BMI < 20 kg/m^2, %	16.3	13.2
Performance status, %		
0-1	80.9	81.5
2	19.1	18.5
ADL score = 6, %	82.1	89.3
IADL score, %		
0	71.7	71.2
1	16.3	20.2
≥ 2	12.0	8.6
Folstein MMSE > 23, %	83.7	85.6
No geriatric syndrome, %	90	91.4
Charlson comorbidity index		
0-1	76.5	75.7
≥ 2	23.5	24.3
GDS5		
0-1	85.7	83.5
2-3	12.7	12.0
4-5	1.6	4.5

Abbreviations: ADL, activities of daily living; BMI, body mass index; CGA, comprehensive geriatric assessment; GDS5, Geriatric Depression Scale 5; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination.

Table 3. Treatments and Outcomes

Treatment and Outcome	Standard Arm (n = 251)	CGA Arm (n = 243)	*P* (Log-Rank Test)
Treatment allocation, No. (%)			< .001
Monotherapy	163 (64.9)	76 (31.3)	
Doublet	88 (35.1)	111 (45.7)	
BSC		56 (23.0)	
Median TFFS, months			.32
All	3.2	3.1	
Doublet	4.4	4.8	
Monotherapy	2.9	2.6	
BSC	—	1.3	
Reasons for treatments failures, No. (%)			
Missing data	14	15	
Progression	156 (65.8)	158 (69.3)	.42
Toxicity	28 (11.8)	11 (4.8)	.01
Toxicity except for BSC in the CGA arm	28 (11.8)	11 (6.3)	.06
Withdrawal of consent	9 (3.8)	7 (3.1)	.67
Death	31 (13.1)	32 (14.0)	.76
Other	13 (5.5)	20 (8.8)	.17
Median PFS, months			.59
All	3.7	3.4	
Doublet	4.7	4.8	
Monotherapy	3.1	2.7	
BSC	—	1.3	
Median OS, months			.87
All	6.4	6.1	
Doublet	8.6	10.0	
Monotherapy	5.7	4.9	
BSC	—	2.8	
Mean life expectancy adjusted on QoL, months	4.3	4.4	.51

Abbreviations: BSC, best supportive care; CGA, comprehensive geriatric assessment; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TFFS, treatment failure–free survival.

2.8 months, respectively (Table 3). Central review of treatment responses, assessable in 75% and 71% of patients in the standard and CGA arms, respectively, showed no difference in the objective response rate (26.6% *v* 26.0%, respectively; $P = .89$) or the disease control rate (80.8% *v* 73.4%, respectively; $P = .09$).

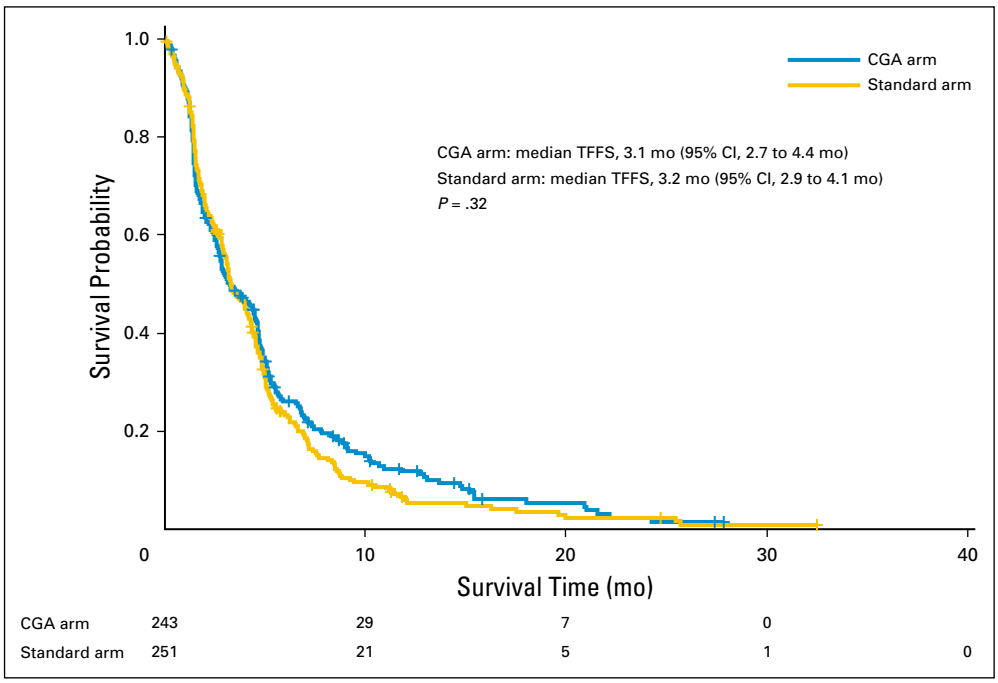

Fig 3. Treatment failure–free survival (TFFS) over the duration of the study. CGA, comprehensive geriatric assessment.

Table 4. Grade 3 or 4 Toxicities

Toxicity	% of Patients: Standard Arm (n = 251)	% of Patients: CGA Arm (n = 243)	*P*
All grades	93.4	85.6	.01
Grade 3-4	71.3	67.9	.41
Grade 3-4 neutropenia			.41
All	11.1	13.2	
Doublet	16.0	25.2	
Monotherapy	8.0	5.3	
BSC	—	0	
Grade 3-4 febrile neutropenia			.22
All	5.6	3.3	
Doublet	11.0	5.4	
Monotherapy	2.4	2.6	
BSC	—	0	
Grade 3-4 anemia			.87
All	11.2	10.7	
Doublet	21.6	16.2	
Monotherapy	5.5	6.6	
BSC	—	5.3	
Grade 3-4 thrombocytopenia			.04
All	3.6	7.8	
Doublet	7.9	17.1	
Monotherapy	1.2	0	
BSC	—	0	
Grades 3-4 asthenia			.34
All	10.8	13.6	
Doublet	7.9	14.4	
Monotherapy	12.3	15.8	
BSC	—	8.9	
Grade 3-4 anorexia			.27
All	4.0	6.2	
Doublet	0	10	
Monotherapy	6.0	5.3	
BSC	—	0	
Grade 3-4 nausea/vomiting			.46
All	3.6	4.9	
Doublet	1.1	8.1	
Monotherapy	4.9	2.6	
BSC	—	1.8	
Grade 3-4 peripheral sensory neuropathy			.62
All	1.2	0.4	
Doublet	0	0	
Monotherapy	1.8	1.3	
BSC	—	0	

Abbreviations: BSC, best supportive care; CGA, comprehensive geriatric assessment.

The percentage of patients who experienced all grade Aes was significantly higher in the standard arm than in the CGA arm (93.4% *v* 85.6%, respectively; $P = .015$), but this difference was no longer significant when the analysis was restricted to grade 3 or 4 Aes (71.3% *v* 67.9%, respectively; $P = .41$). The most common grade 3 or 4 Aes were neutropenia, anemia, and asthenia (Table 4). QoL utility scores at baseline did not differ between the arms. At each subsequent evaluation, the utility score was always higher in the CGA arm than in the standard arm (data not shown), but the difference was significant only at week 36 ($P = .02$). Utility scores tended to decline over time and were not significantly different between the arms ($P = .85$). Life expectancies adjusted on QoL were 4.3 and 4.4 months in the standard and CGA arms, respectively (Table 3). Several factors negatively influenced TFFS in univariate analysis (Appendix Table A3, online only), but only body mass index ≤ 20 kg/m^2, former or current smoking status, less than four chemotherapy cycles, Charlson comorbidity index ≥ 2, and the existence of a geriatric syndrome remained independent unfavorable prognostic factors for TFFS in multivariate analysis.

DISCUSSION

To our knowledge, this is the first randomized trial in which a CGA was integrated into the treatment allocation for elderly patients with advanced NSCLC and that prospectively studied its impact on survival outcomes. The Elderly Selection on Geriatric Index Assessment (ESOGIA) study demonstrates the feasibility of CGA in a large cohort of elderly patients, although no resulting improvement in TFFS or OS was observed. Several explanations for these negative results can be envisaged. First, TFFS is a combined primary end point particularly adapted to elderly patients, taking into account not only progression but also tolerability.[24] This is a good option for cancers with an indolent course or in case of patients with significant comorbidities who are likely to die of causes other than cancer. However, as was the case in this study, patients with NSCLC are more likely to have treatment interruptions as a result of progressive disease or death and less likely as a result of toxicity. Second, even if more patients in the CGA arm received a carboplatin doublet, the difference compared with the standard arm was small (Table 3) and was counterbalanced by the 23% of patients who received BSC alone. (Appendix Table A4 [online only] indicates what would have been the allocations of treatment based on CGA parameters in the standard arm.) Moreover, the cutoffs used to define fit, vulnerable, and frail patients may not be the most relevant in the advanced NSCLC setting, even if the domains explored here were consistent with recent recommendations.[18] The impact of comorbidities on outcome could be lesser in patients with advanced NSCLC, most of whom die of NSCLC rather than comorbidities. Nevertheless, comorbidities provide information independent of functional status; they are associated with worse survival among elderly patients with advanced NSCLC and also with a variety of other tumors.[11,25,26] In our study, a Charlson comorbidity index ≥ 2 and the presence of a geriatric syndrome were unfavorable independent predictors of TFFS in multivariate analysis. The type and severity of comorbidities, rather than just their number, should probably be considered for treatment allocation in this setting.

CGA on the basis of the ADL and instrumental ADL scores adds substantial information to functional assessment on the basis of PS alone.[18,27] Maione et al[28] demonstrated that the instrumental ADL score but not the ADL score had independent prognostic value for survival, especially in frail patients. However, neither score was an independent prognostic factor for TFFS in our multivariate analysis. One possible drawback in our definition of the CGA groups is that we did not integrate nutritional parameters. Indeed, body mass index ≤ 20 kg/m^2 was an independent unfavorable prognostic factor for TFFS in multivariate analysis, and recent studies have shown that poor nutritional status is associated with a poor prognosis in elderly patients with cancer.[29,30] As suggested by previous studies, geriatric assessment might help with the choice of well-tolerated treatments.[18] The

patients in the CGA arm showed a modest but statistically significant lower incidence of all grade Aes and treatment failures as a result of toxicity (Table 3), possibly because 23% of them received BSC alone. Nevertheless, a nonsignificant difference persisted when patients who received BSC were excluded from the analysis (6.3% *v* 11.8% in CGA and standard arms, respectively), even though more and older patients received doublet therapy in the CGA arm. The median OS among fit patients treated with a carboplatin doublet in the CGA arm was 10.0 months, in line with median values reported in previous studies including fit elderly patients with advanced NSCLC treated with various carboplatin doublets.[9,31] In our study, these fit patients had a favorable safety profile, with grade 3 or 4 neutropenia, febrile neutropenia, and treatment-related death in 23.8%, 5.5%, and 0.9% of patients, respectively; the corresponding rates were 48.4%, 9.4%, and 4.4%, respectively, among the 225 patients treated with carboplatin-paclitaxel in the Intergroupe Francophone de Cancérologie Thoracique 05.01 trial.[9] Our favorable results may be related to the chemotherapy regimens used, but the median OS among the 88 patients in the standard arm (all ≤ 75 years old) was 8.6 months, and the toxicity profile was similar, suggesting that CGA can help to select fit elderly patients who can be treated safely and effectively with a carboplatin-based doublet. The 73 vulnerable patients treated with weekly docetaxel in the CGA arm had a short median OS of 4.9 months, compared with 5.1 to 8.5 months in trials of first-line single-agent chemotherapy.[3,21,32,33] This difference may be a result of subsequent-line treatments but also of the fact that patients in the CGA arm were selected according to frailty criteria. As a matter of fact, median OS was better (5.7 months) among patients treated by docetaxel in the standard arm and selected on the basis of PS and age. Median OS among frail patients managed exclusively with BSC was only 2.8 months, which clearly is lower than the OS of 5.2 months among patients ≥ 70 years old with a PS of 0 to 2 who received BSC alone in the Elderly Lung Cancer Vinorelbine Italian Study trial.[3] This suggests that the CGA identified patients with a poor natural prognosis, but our study design did not allow us to validate the appropriateness of exclusive BSC for these patients. Interestingly, although Qol utility scores at baseline were not different between the arms, they always were higher (although not significantly so) in the CGA arm than in the standard arm at each subsequent evaluation, with no evident negative impact of the 23% of patients who received exclusive BSC.

In our study, as recommended in 2009, none of the patients ≥ 75 years old in the standard arm or with a PS of 2 in either arm received a carboplatin doublet. However, recent trials have shown that selected patients ≥ 75 years old and/or with a PS of 2 can be treated with a carboplatin doublet.[9,34] As a consequence, some of these patients may have been undertreated in both arms, and geriatric parameters in the CGA arm could have had less impact on the treatment allocation.

CGA-based allocation of chemotherapy did not improve the survival outcomes of elderly patients with advanced NSCLC. Consequently, the use of CGA in this setting cannot be routinely advised in clinical practice. Further research is needed to better identify within CGA the most relevant tools in patients with advanced NSCLC.

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Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC-GECP 08-02 Study

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Appendix

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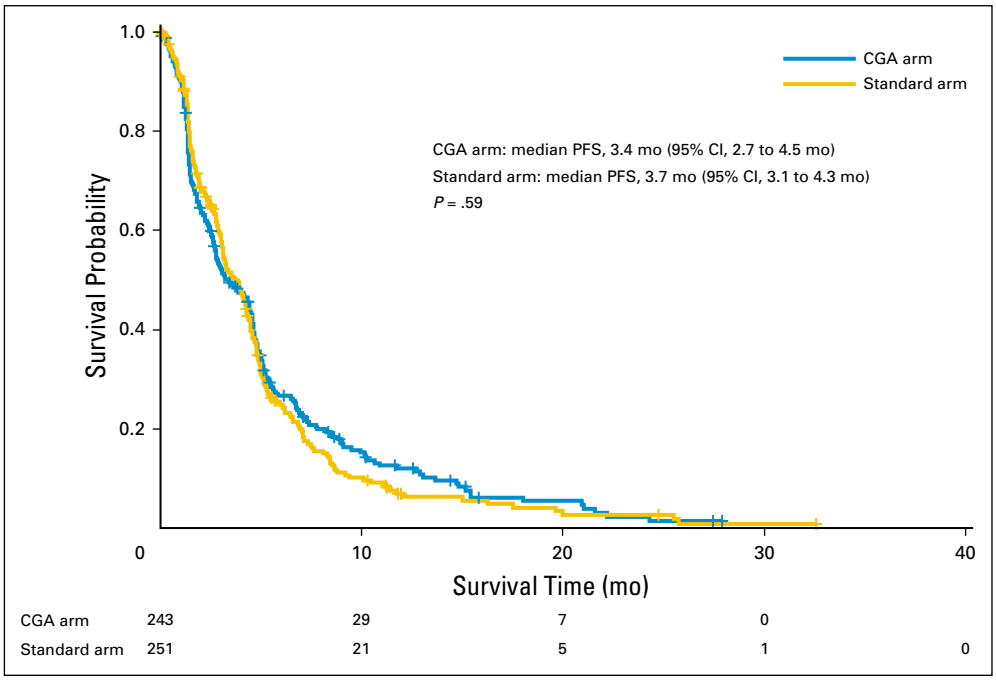

Fig A1. Progression-free survival (PFS) over the duration of the study. CGA, comprehensive geriatric assessment.

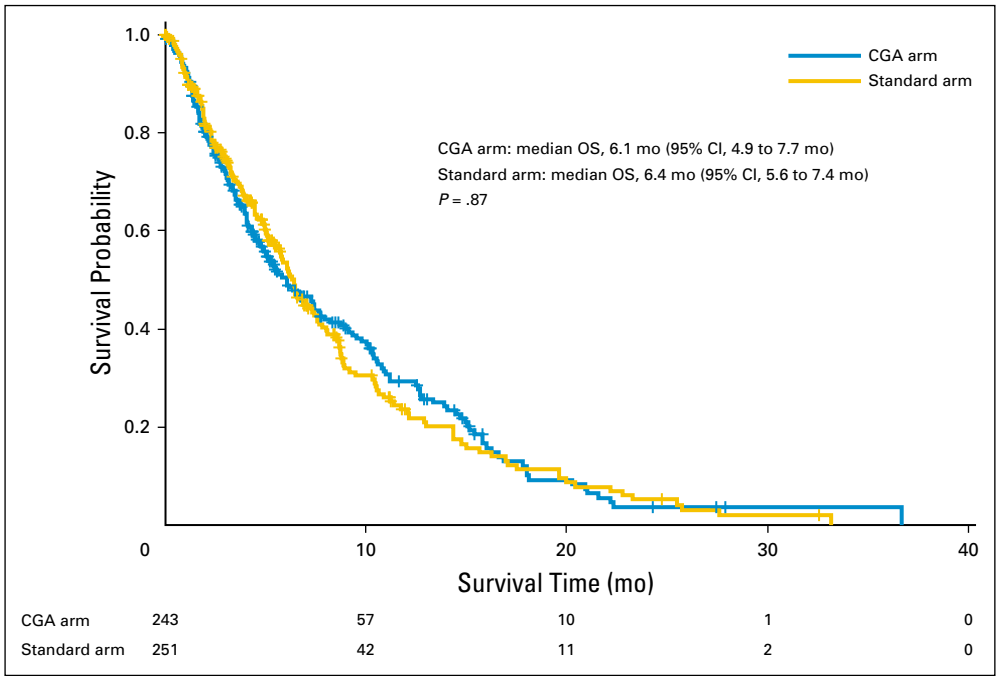

Fig A2. Overall survival (OS) over the duration of the study. CGA, comprehensive geriatric assessment.

Table A1. Domains Explored by the Comprehensive Geriatric Assessment

Domain	Scales
Functional status	Eastern Cooperative Oncology Group performance status, Katz basic Activities of Daily Living Scale, Simplified Lawton's Instrumental Activities of Daily Living Scale
Comorbidities	Charlson comorbidity index
Medications	Number, type, indication
Cognitive function	Folstein Mini-Mental State Examination, Schultz-Larsen Mini-Mental State Examination
Geriatric syndrome	Repeated falls, fecal and/or urinary incontinence
Depression/ mood	Geriatric Depression Scale 5, Emotional questionnaire
Nutrition	Body mass index
Mobility	Timed Up and Go test
Situational assessment	Accessibility of services, mobility, social environment, accessibility of home rooms

Table A2. Treatment Received After Progression

Treatment	% of Patients	
	Standard Arm (n = 251)	CGA Arm (n = 243)
Patients who received second-line treatment	40.6	41.1
Patients who received a second-line treatment according to the first-line treatment received		
Monotherapy	37.3	39.6
Carboplatin doublet	50	55
BSC	—	17.6
Types of second-line treatment received		
Tyrosine kinase inhibitor	69.5	66.6
Pemetrexed monotherapy	14.5	15.3
Gemcitabine, docetaxel, or vinorelbine monotherapy	16	18.1

Abbreviation: BSC, best supportive care.

Table A3. Univariate and Multivariable Analyses of Treatment-Failure-Free Survival

Variable	No. of Patients	Univariate Analysis		Multivariable Analysis	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Arm					
Standard arm	251	1		—	—
CGA arm	243	0.91 (0.76 to 1.1)	.3231	—	—
BMI (kg/m^2)					
20-25	223	1		1	
≤ 20	73	1.56 (1.19 to 2.05)	.0014	2.38 (1.53 to 3.71)	.0001
26-30	123	1.07 (0.85 to 1.35)	.5803	1.12 (0.79 to 1.58)	.5288
> 30	39	0.82 (0.57 to 1.18)	.2874	1.09 (0.65 to 1.82)	.7453
Smoker status					
Never-smokers	74	1		1	
Former smokers	60	1.17 (0.81 to 1.7)	.3935	1.97 (1.18 to 3.31)	.0098
Current smokers	233	1.38 (1.05 to 1.819)	.0216	1.71 (1.16 to 2.53)	.0071
No. of chemotherapy cycles					
< Four	149	1		1	
Four	276	0.34 (0.28 to 0.42)	< .0001	0.28 (0.20 to 0.38)	< .0001
Treatment					
Monotherapy	239	1		—	—
Carboplatin doublet	199	0.67 (0.55 to 0.82)	< .0001	—	—
Best supportive care	56	1.51 (1.11 to 2.04)	.0084	—	—
Albumin (g/L)					
> 30	94	1		—	—
≤ 30	254	1.7 (1.33 to 2.17)	< .0001	—	—
ECOG PS					
0	136	1		—	—
1	265	1.35 (1.08 to 1.68)	.0079	—	—
2	93	2.72 (2.05 to 3.60)	< .0001	—	—
ADL score					
0	423	1		—	—
≥ 1	71	1.53 (1.18 to 1.98)	.0012	—	—
IADL score					
0	353	1		—	—
1	90	1.27 (0.99 to 1.63)	.0565	—	—
≥ 2	51	2.77 (2.05 to 3.75)	< .0001	—	—
Charlson comorbidity index					
0	215	1		1	
1	161	1.17 (0.95 to 1.45)	.1489	1.10 (0.79 to 1.53)	.5705
≥ 2	118	1.72 (1.36 to 2.18)	< .0001	1.75 (1.17 to 2.62)	.0064
GDS 5 score					
0-1	417	1		—	—
2-3	61	1.47 (1.1 to 1.96)	.0089	—	—
4-5	15	1.68 (0.98 to 2.87)	.0571	—	—
Folstein's MMSE score					
> 23	418	1		—	—
≤ 23	76	1.46 (1.13 to 1.89)	.0037	—	—
Falls during the last year					
No	420	1		—	—
Several	24	1.77 (1.16 to 2.7)	.0081	—	—
One	50	1.24 (0.91 to 1.70)	.1686	—	—
Continence					
Yes	469	1		1	
No	25	1.39 (0.92 to 2.09)	.1200	5.15 (1.84 to 14.46)	.0013
Recent weight loss (at least 3 kg)					
No	215	1		—	—
Yes	270	1.33 (1.1 to 1.61)	.0029	—	—
Loss of appetite					
No	429	1		—	—
Yes	65	1.54 (1.17 to 2.03)	.0022	—	—
Get up and go test					
Normal	359	1		—	—
Abnormal	132	1.3 (1.05 to 1.6)	.0140	—	—
Autonomy					
Yes	409	1		—	—
No	83	1.96 (1.53 to 2.52)	< .0001	—	—

(continued on following page)

Table A3. Univariate and Multivariable Analyses of Treatment-Failure-Free Survival (continued)

Variable	No. of Patients	Univariate Analysis		Multivariable Analysis	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Social environment					
Good social environment	440	1		—	—
Social isolation/insufficient environment	54	1.35 (1.01 to 1.81)	.0442	—	—

NOTE. All baseline variables with $P < .20$, univariate Cox model were included in the multivariate analysis, but only the "best subset of predictors" were retained in the final model after stepwise selection. Dashes indicate nonsignificant results.

Abbreviations: ADL, Activities of Daily Living; BMI, body mass index; CGA, comprehensive geriatric assessment; ECOG PS, Eastern Cooperative Oncology Group performance status; GD5, Geriatric Depression Scale 5; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination.

Table A4. Allocations of Treatment Based on CGA Parameters in the Standard Arm

Treatment based on CGA	Treatment Based on PS and Age	
	Single Therapy (n = 163), No. (%)	Double Therapy (n = 88), No. (%)
Double-agent therapy	51 (31.3)	45 (51.1)
Single-agent therapy	37 (22.7)	19 (21.6)
Best supportive care	75 (46.0)	24 (27.3)

Abbreviations: CGA, comprehensive geriatric assessment; PS, performance status.

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Chemotherapy completion in elderly women with ovarian, primary peritoneal or fallopian tube cancer – An NRG oncology/Gynecologic Oncology Group study☆,☆☆,☆☆☆

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HIGHLIGHTS

- IADL was correlated with completion of 4 cycles of chemotherapy.
- ADL, social activity, and QOL improved over time.
- IADL was associated with overall survival in those receiving CP.

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ABSTRACT

Purpose. A simple measure to predict chemotherapy tolerance in elderly patients would be useful. We prospectively tested the association of baseline Instrumental Activities of Daily Living (IADL) score with ability to complete 4 cycles of first line chemotherapy without dose reductions or >7 days delay in elderly ovarian cancer patients.

Patients and methods. Patients' age ≥70 along with their physicians chose between two regimens: CP (Carboplatin AUC 5, Paclitaxel 135 mg/m^2) or C (Carboplatin AUC 5), both given every 3 weeks either after primary surgery or as neoadjuvant chemotherapy (NACT) with IADL and quality of life assessments performed at baseline, pre-cycle 3, and post-cycle 4.

Results. Two-hundred-twelve women were enrolled, 152 selecting CP and 60 selecting C. Those who selected CP had higher baseline IADL scores ($p < 0.001$). After adjusting for age and PS, baseline IADL was independently associated with the choice of regimen ($p = 0.035$). The baseline IADL score was not found to be associated with completion of 4 cycles of chemotherapy without dose reduction or delays ($p = 0.21$), but was associated with completion of 4 cycles of chemotherapy regardless of dose reduction and delay ($p = 0.008$) and toxicity, with the odds ratio (OR) of grade 3+ toxicity decreasing 17% (OR: 0.83; 95%CI: 0.72–0.96; $p = 0.013$) for each additional activity in which the patient was independent. After adjustment for chemotherapy regimen, IADL was also associated with overall survival ($p = 0.019$) for patients receiving CP.

Conclusion. Patients with a higher baseline IADL score (more independent) were more likely to complete 4 cycles of chemotherapy and less likely to experience grade 3 or higher toxicity.

1. Introduction

With the aging of a large cohort of baby boomers, it is anticipated that the frequency of age-related cancers such as ovarian cancer will grow, and we will be treating more elderly patients with the disease, including the "oldest of old" [1]. It has been claimed that many elderly women with ovarian cancer are not being provided with "appropriate" care, including standard doses and schedule of chemotherapy, and that this may partially account for their inferior cancer outcomes [2]. However, it is also known that older patients suffer more toxicity from chemotherapy, and that there is great heterogeneity in ability of patients of a given chronological age to tolerate treatment. There would be great value in a simple assessment to help the clinician predict the ability of a patient to tolerate chemotherapy as well as to potentially allow some comparison of functional status among elderly patients treated on clinical trials.

Numerous studies have demonstrated that chronological age does not equal physiological age. A geriatric assessment and patient reported outcomes (PROs) can be utilized to assess for the heterogeneity of functional abilities among older patients with cancer. A geriatric assessment includes an evaluation of functional status, comorbid medical conditions, psychological state, social support, nutritional status, and cognition [3]. An assessment of functional status includes evaluating the patient's ability to perform Instrumental Activities of Daily Living (IADLs) which are self-care skills that allow independent functioning within the community and Activities of Daily Living (ADLs) which are basic self-care skills such as the ability to bathe and dress. PROs are questionnaires used in a clinical setting or trial where the responses are collected directly from the patient [4]. The most commonly used PRO tools assess symptoms, functional status, and quality of life (QOL).

The primary objective of this study was to explore the association between pre-treatment Instrumental Activities of Daily Living (IADL) and the patient's ability to complete 4 cycles of chemotherapy without dose reduction or >7-day treatment delay for patients aged 70 years and older with primary ovarian, peritoneal, or fallopian tube cancer. Four cycles were chosen to allow patients to receive chemotherapy before or after surgery. Secondary objectives included exploring whether age, geriatric measures and patient-related outcomes (PROs) were correlated with toxicity or completion of chemotherapy. Translational research objectives included exploring the relationship between actual and calculated carboplatin AUC and the relationship between pharmacokinetic parameters and toxicity.

2. Methods

2.1. Patients

Eligible patients were ≥70 years of age with stage I-IV epithelial cancer of the ovary, peritoneum, or fallopian tube. The cancer diagnosis was to be histologically or cytologically confirmed by surgery, biopsy, fine needle aspiration or paracentesis. A diagnosis of a mucinous cancer could be made by biopsy only. Patients were required to have received no previous treatment for the malignancy, a Gynecologic Oncology Group (GOG) performance status (PS) of 0 to 3, normal blood, renal and hepatic function. All patients gave written informed consent according to institutional and federal guidelines before enrollment and the institutional review board at each participating site granted approval.

Patients could be registered either before primary chemotherapy or after cytoreduction surgery, prior to adjuvant chemotherapy. At study entry and before each treatment, a physical examination, medical history, and laboratory measurements were recommended. Patient-reported assessments (PROs) and physician assessment of PS were required prior to cycle 1 and 3, then 3–6 weeks after completion of cycle 4.

2.2. Treatment plan

Patients and physicians selected between two chemotherapy options. There was no randomization. CP was carboplatin AUC 5 plus paclitaxel 135 mg/m^2 plus pegfilgrastim or filgrastim (G-CSF) every 3 weeks. The G-CSF was initially required, but was changed to optional in February 2013. C was single agent carboplatin AUC 5 on day 1, every 3 weeks. Patients on either arm for whom the treating physician felt a carboplatin AUC of 5 to be unsafe could be started with a carboplatin AUC of 4. Standard dose modifications and parameters for treatment were suggested, but not required. After 4 cycles of chemotherapy, interval surgical cytoreduction (for patients who did not have prior primary surgery), and/or further chemotherapy were at the discretion of the treating physician.

2.3. Quality of life and other assessments

The Functional Assessment of Cancer Therapy – Ovary (FACT-O), is a multi-dimensional PRO used to measure quality of life (QOL) [5]. It is composed of 4 subscales (physical well-being, social well-being, emotional well-being, and functional well-being). A higher score represents

better QOL. The FACT/GOG-Ntx-4 subscale was used to assess peripheral neuropathy [6]. The Instrumental Activities of Daily Living (IADL) assessment used is a subscale of the Older American Resources and Services tool (OARS) [7]. This assessment provides a profile of the level of functioning and need for services in community-dwelling older adults. A higher IADL score indicates more independence. Activities of Daily Living (ADL) were measured using a subscale of the Medical Outcomes Study (MOS) Physical Health assessment [8]. Higher scores indicate more independence in ADL. The social activities subscale from the MOS was used in measuring social activity. Higher scores indicate less limitation in social activities. Medical comorbidity was measured with the Charlson Comorbidity Index [9]. The calculation for % unintentional weight loss was calculated = (weight lost in last 6 months/baseline body weight) × 100.

2.4. Pharmacokinetic methods

Blood samples for quantitation of platinum concentrations were obtained at baseline and at 24 h after carboplatin infusion. Blood samples for quantitation of paclitaxel were obtained at baseline, 1, 6, and 24 h after infusion. At each time point, 7–10 mL of EDTA anticoagulated blood was drawn, inverted 5–10 times and placed on ice. Blood was then centrifuged at 1000 ×*g* for 10 min at 4 °C, and plasma was aliquoted in cryovials and frozen at −70 °C or colder. Concentrations of total platinum were quantitated by atomic absorption spectrophotometry [10]. Concentrations of paclitaxel were determined using an established assay [11]. The AUC of ultrafilterable platinum was estimated utilizing the total platinum concentration at 24 h [12]. Paclitaxel AUC and time above 0.05 μM were also estimated with a previously published formula [13].

2.5. Statistical analysis

The primary objective of this study was to explore the association between patient-reported IADL at baseline and the ability to complete 4 cycles of chemotherapy without dose reduction or >7 days treatment delay (tolerance of chemotherapy). A sample size of 185 patients was planned to provide an 80% statistical power at a 5% significant level to detect a 10% increase in the tolerance when a patient's baseline IADL is one standard deviation higher than the mean score (two-tailed test). It was assumed that approximately 70% would complete 4 cycles of treatment without delay and dose reduction and the r^2 achieved when IADL is regressed on other covariates was no larger than 0.3. The study was initially targeted to elderly patients who were at least 75 years old. Due to concerns about slow accrual, the age criteria for this study were altered from ≥75 to ≥70 years in April 2012. To ensure that the study sample was representative of elderly patients in all age groups we limited the patients aged 70–74 to approximately 25% of the total enrolled.

The completion status of 4 cycles was summarized for all eligible patients (n = 207) who received at least 1 cycle. The analysis of the association between baseline PROs and tolerance was based on patients who completed baseline assessments. The analysis of the PROs over time was based on patients who completed baseline and at least 1 follow up assessment. A logistic regression was used in evaluating the likelihood of completing 4 cycles, the type of chemotherapy, and the development of grade 3+ toxicities.

The baseline IADL score was examined first as a continuous variable for its association with tolerance of chemotherapy. We also explored the IADL based on the number of activities, which was considered supportive to the primary analysis. The number ranged 0–7 with 0 = dependent and 7 = independent. The association between baseline IADL and overall survival (OS) was explored with Cox proportional hazards model. A linear mixed model was used in exploring the change of PRO and QOL over assessment time. Subgroup analysis based on the chemotherapy regimen chosen was conducted for exploratory purposes.

The primary endpoint of this study was the IADL score as a continuous variable and its association with the completion of 4 cycles of chemotherapy without dose reduction and >7 days delay was tested at a predesigned significant level of 5%. Other analyses were considered exploratory and were not corrected for multiple testing. The p values for the exploratory analyses were provided to aid interpretation but must be interpreted conservatively. We considered p values of 0.01–0.05 to reflect a modest association and $p < 0.01$ to reflect a significant association.

3. Results

3.1. Patient population

Between August 15, 2011 and August 12, 2013, a total of 212 patients selected between 2 treatment options and were enrolled on study. Five were excluded from the analysis, due to protocol violation (Appendix Fig. A1, online only). The characteristics of the 207 evaluable (CP, n = 148; C, n = 59) patients are summarized in Table 1. The average age was 77 years (70–89) for regimen CP and 84 (71–98) for regimen C. There were no significant differences in race and stage between the cohorts. Patients selecting CP were younger ($p < 0.001$) and had better PS ($p = 0.001$); higher IADL ($p < 0.001$), ADL ($p < 0.001$), QOL ($p = 0.04$) and less comorbidity ($p = 0.08$). After adjusting for age and PS, baseline IADL score was independently associated with the choice of regimen ($p = 0.035$). There were 73 patients in the CP cohort and 35 in C cohort who were treated initially with chemotherapy. Of these 52% in the CP cohort and only 6% in the C cohort had surgery after chemotherapy.

Table 1
Patient characteristics at baseline. Carboplatin Paclitaxel = CP, Carboplatin = P. AUC = Area under the curve, QOL = quality of life, BMI = body mass index, FACT-O = The Functional Assessment of Cancer Therapy – Ovary.

		CP (n = 148)		C (n = 59)		Total (n = 207)	
Characteristic	Category	No.	%	No.	%	No.	%
Age categories	70–74	51	34	4	7	55	27
	75–79	59	40	12	20	71	34
	80–84	30	20	20	34	50	24
	≥85	8	5	23	39	31	15
Race	Non-hispanic black	12	8	2	3	14	7
	Non-hispanic white	133	90	55	93	188	91
	Other	3	2	2	3	5	2
Performance status	0	67	45	17	29	84	41
	1	62	42	21	36	83	40
	2	14	9	13	22	27	13
	3	5	3	8	14	13	6
Stage	I	8	5	1	2	9	4
	II	13	9	5	8	18	9
	III	98	66	44	75	142	69
	IV	29	20	9	15	38	18
Neoadjuvant chemo	No	75	51	24	41	99	48
	Yes	73	49	35	59	108	52
Carboplatin dosage	AUC 4	8	5	6	10	14	7
	AUC 5	140	95	53	90	193	93
GCSF use	Start with cycle 1	118	80	–			
	Start post cycle 1	9	6	–			
	No	21	14	–			
Geriatric and QOL assessment at baseline		Mean (Range)		Mean (Range)		Mean (Range)	
Instrumental Activities of Daily Living (IADL)		12 (4–14)		10 (2–14)		12 (2–14)	
Activities of Daily Living (ADL)		46 (0–100)		38 (0–100)		42 (0–100)	
No. of falls in last 6 months		0.4 (0–7)		0.4 (0–4)		0 (0–7)	
No. of medical morbidities		0.7 (0–4)		1.0 (0–6)		1 (0–6)	
Social activities		54 (6–94)		47 (6–94)		52 (6–94)	
BMI		27 (16–40)		27 (18–49)		27 (16–49)	
% Weight loss in last 6 months		6 (−23–33)		3 (−17–30)		5 (−23–33)	
Quality of life measured with FACT-O		111 (54–151)		106 (66–145)		110 (54–151)	

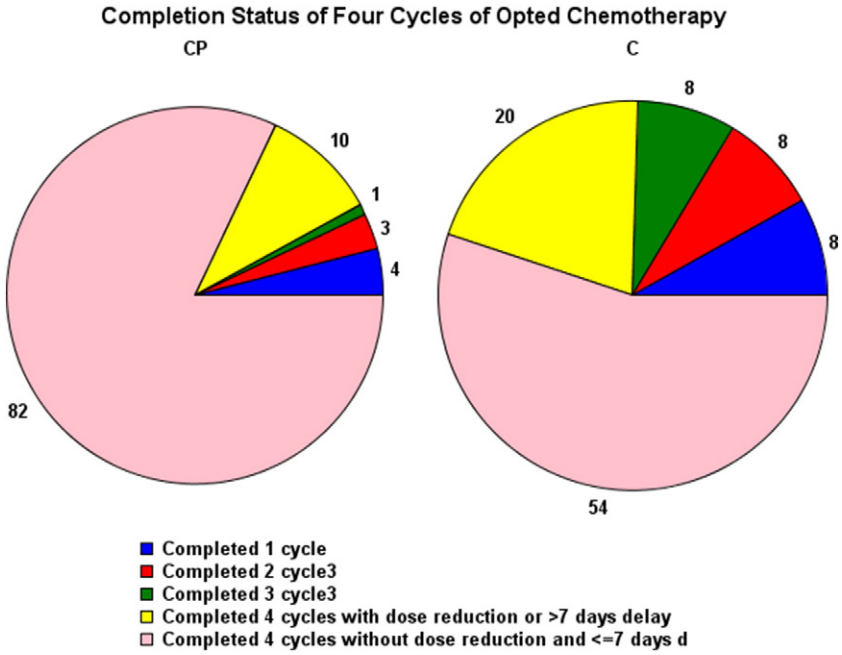

Fig. 1. Completion status of four cycles of chemotherapy. Carboplatin Paclitaxel = CP, Carboplatin = P. Numbers equal %.

3.2. Chemotherapy completion and adverse events

Seventy-four percent of patients completed 4 cycles without dose reduction or more than a 7-day treatment delay and 87% completed 4 cycles of chemotherapy regardless of reduction or delay (Fig. 1). Eighty-two percent in CP and 54% in C completed 4 cycles of chemotherapy without either reduction or >7-day delay. A total of 92% in the CP arm and 75% in C eventually completed 4 cycles. Choice of CP was

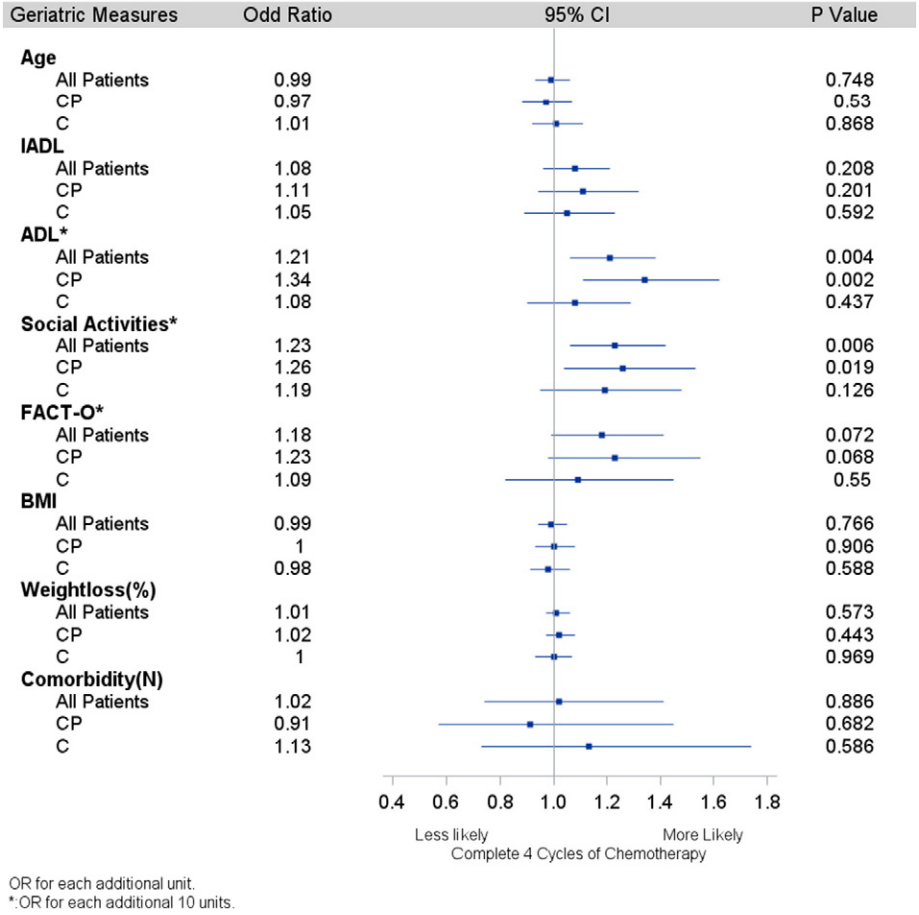

Fig. 2. Subgroup analysis of the association between other geriatric measures and tolerance of chemotherapy. Independent activities of daily living (IADL), activities of daily living (ADL), The Functional Assessment of Cancer Therapy – Ovary (FACT-O), body mass index (BMI).

significantly correlated ($p < 0.001$) with the likelihood of completing 4 cycles of chemotherapy without dose reduction or >7-day delay. After adjusting for chemotherapy regimen, age and stage were not found to be associated with likelihood of completing 4 cycles without dose reduction or delay.

The median treatment delay was 7 days with a range of 1–28 days. Paclitaxel hypersensitivity ($n = 7$) was the major reason for dose reduction in CP while hematologic toxicity was the primary reason in regimen C. In CP, 3 discontinued chemotherapy for side effects and 5 for other issues. In the C cohort, 5 discontinued for disease progression, 1 for side effects and 6 for other issues.

Significantly more patients who received CP had adverse events (Appendix Table A1, online only). For CP the most common grade ≥ 3 side effect was decreased neutrophil count (13%), followed by anemia, diarrhea, and dehydration. For C, the most common grade ≥ 3 side effect was anemia (12%), followed by fatigue and thrombocytopenia. There were 7 deaths on study, 4 on CP and 3 on C. One death on the CP regimen was attributed to treatment, 1 to treatment and disease, 1 to cardiac arrest, and 1 to aspiration. The patient who died due to treatment had extensive disease with questionable progression along with bone marrow and gastrointestinal toxicity and she was not given GCSF. The 3 deaths on regimen C were secondary to disease.

3.3. Association between baseline IADL and completion of chemotherapy

There were 205 patients who completed PROs at baseline. The baseline IADL score was 12 (SD: 2.6; range: 2–14) for those who completed 4 cycles without dose reduction or more than 7-day delay and 11 (SD: 2.9; range; 3–14) for those who did not. The IADL score was not found to be associated with completion of 4 cycles of chemotherapy without reduction or more than 7-day delay ($p = 0.208$), (Fig. 2). However, patients with a higher IADL ($p = 0.008$), ADL ($p = 0.002$), social activities score ($p = 0.001$) and QOL score ($p = 0.002$), were more likely to complete 4 cycles of therapy regardless of dose reduction and delay (Fig. 3). The odds ratio was 1.21 for completion of 4 cycles (95% CI: 1.05– 1.4; $p = 0.008$) for each additional activity in which the patient was independent. Subgroup analysis by the chemotherapy cohort showed similar trends in both cohorts.

At baseline, 32% (65/205) of patients (36% in CP and 20% in C) reported being independent in all 7 IADLs. Patients with higher IADL scores were more likely to select or advised by their physician to receive CP than those with more dependency ($p < 0.001$). The odds ratio for selection of CP was 1.31 (95% CI: 1.06– 1.61; $p = 0.011$) for each additional independent instrumental activity.

3.4. Association between baseline IADL and development of grade 3 + toxicities

IADL score was found to be associated with development of grade 3 + toxicities during treatment after adjustment for chemotherapy choice. The rate of grade 3 + toxicity decreased 17% (OR: 0.83; 95% CI: 0.72– 0.96; $p = 0.013$) for each additional activity in which the patient was independent.

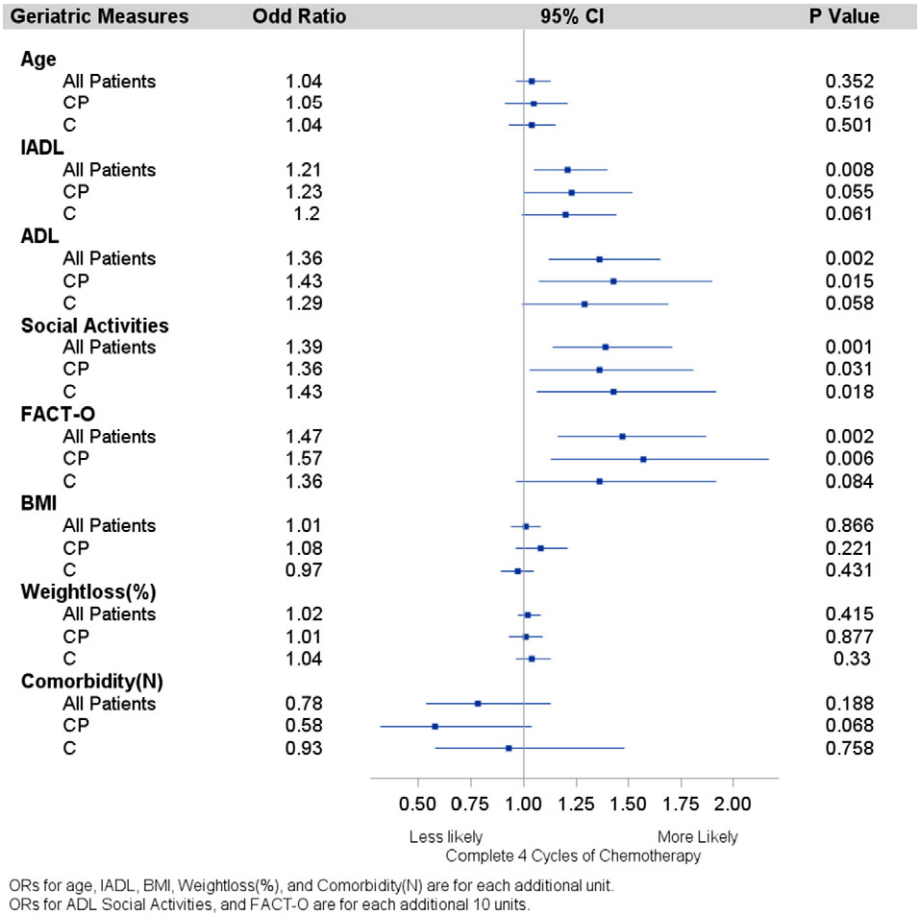

Fig. 3. Subgroup analysis of the association between geriatric measures and four cycles of chemotherapy regardless of dose reduction or treatment delay.

3.5. Association between other assessments and chemotherapy completion

Baseline scores on other assessments were explored for their association with the tolerance after adjusting for the chemotherapy regimen. The completion of 4 cycles without >7-day delay or dose reduction was found to be associated with ADL ($p = 0.002$), and social activities ($p = 0.019$) in patients on CP (Fig. 2). Completion of 4 cycles of therapy regardless of dose reduction and delay was significantly associated with ADL ($p = 0.015$) and QOL ($p = 0.002$) in CP, and with social activities score ($p = 0.001$) in both cohorts (Fig. 3).

3.6. Patient-reported outcomes over time

Of the 207 patients, 190 (139 on CP and 51 on C) completed baseline and at least 1 subsequent PRO. After adjusting for age, PS, and treatment choice, ADL ($p = 0.02$), social activity ($p = 0.04$), and FACT-O ($p < 0.001$) improved over time, but the IADL score did not change ($p = 0.7$). The changes in IADL, ADL, social activities and FACT-O scores exhibited similar trends in both cohorts (Fig. 4). Neurotoxicity worsened significantly for those on CP ($p < 0.001$) but not for those on C ($p = 0.8$).

3.7. Association between baseline IADL and overall survival

After adjustment for chemotherapy, the number of IADLs was associated with OS ($p = 0.019$), (Fig. 5). Subgroup analysis showed this association was only present among patients who received CP ($p = 0.013$). In the CP arm, 45 patients had the ability to independently perform $<= 4$ IADLs while 101 patients had the ability to independently perform $>= 5$ IADLs at baseline. The patients with $<= 4$ independent IADLs were more likely to be non-hispanic black (20% vs 3%), have worse performance status (as measured with the GOG performance status score) ($>= 2$) (29% vs 5%), and have stage IV disease (29% vs 16%) compared to those reporting $>= 5$ independent IADLs.

3.8. Pharmacokinetic analysis

A total of 167 eligible patients (120 in CP and 47 in C) submitted plasma specimens. Specimens from 114 patients on CP were adequate for analysis of paclitaxel and the specimens of 146 patients were adequate for carboplatin levels (Fig. 6). The estimated carboplatin AUC of patients who were intended to receive AUC 5 centered on AUC 5 (mean 5.6), although there was large variability of exposures with a standard deviation of 2.1 (Appendix Table A3, online only). Despite BSA-based dosing of paclitaxel, the observed AUC and clearance covered an almost 10-fold range centered on means of 14.8 ($\pm$4.8) μM * h and 31.7 ($\pm$10.2) h, respectively. After adjustment for baseline ANC and PLT counts, none of the pharmacokinetic properties of paclitaxel and carboplatin was found to be associated with the declined ANC or PLT post cycle 1 (prior to cycle 2). None of the estimated paclitaxel PK parameters correlated with severity of neurotoxicity (Appendix Table A2, online only).

4. Discussion

Our trial was negative for the primary hypothesis of an association of a patient's baseline IADL with the ability to complete 4 cycles of chemotherapy without either dose reduction or >7 days delay. However, there was a significant correlation between IADL score and completion of chemotherapy regardless of reduction or delay,

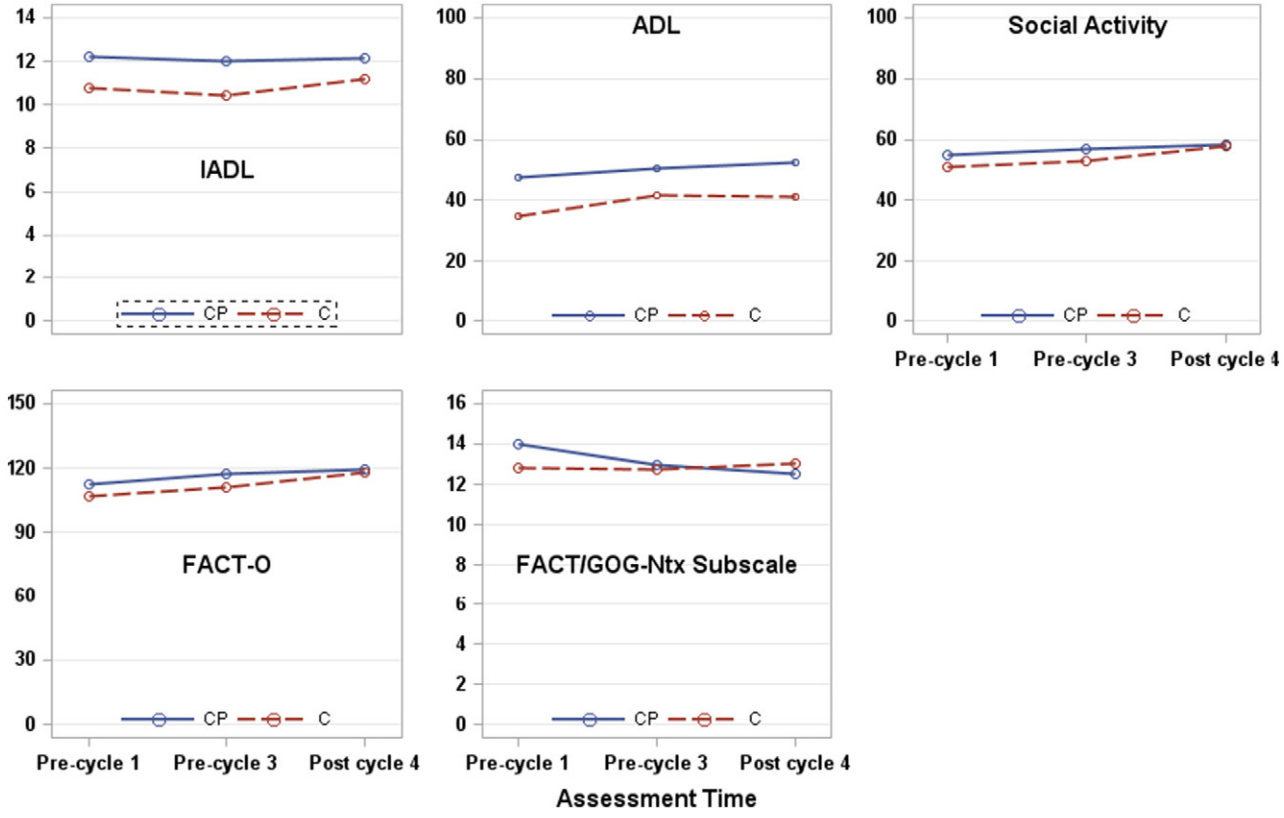

Fig. 4. Patient reported PROs over Time by chemotherapy. Independent activities of daily living (IADL), activities of daily living (ADL), The Functional Assessment of Cancer Therapy – Ovary (FACT-O), Functional Assessment of Cancer Treatment – Neurotoxicity -FACT/GOG-Ntx 4 subscale.

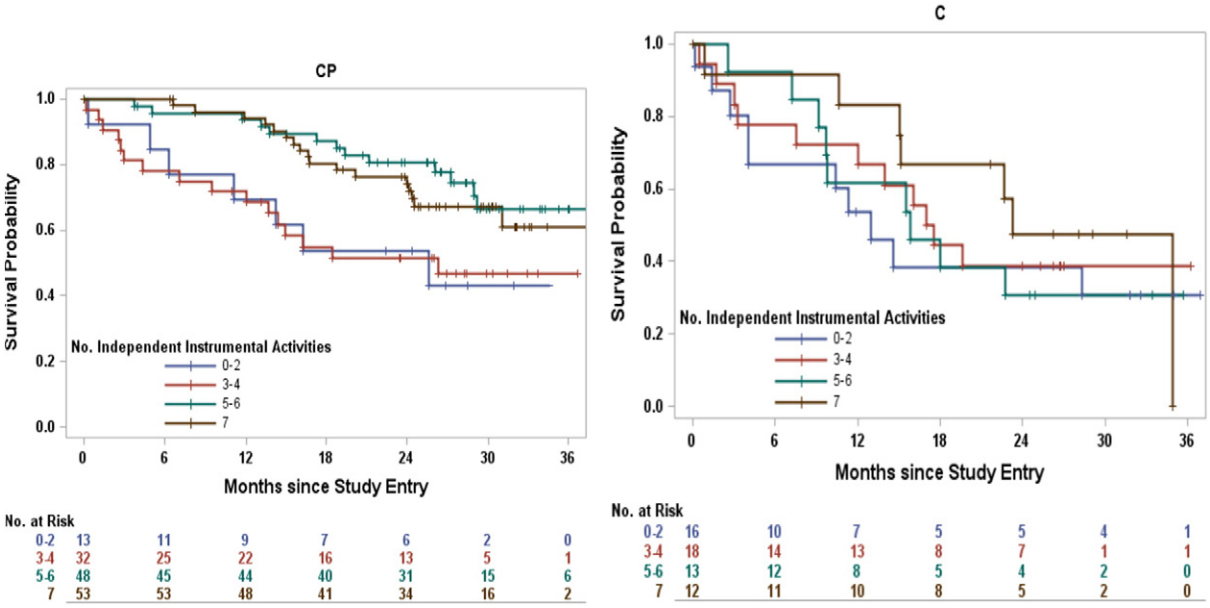

Fig. 5. Overall survival by number of independent instrumental activities. Carboplatin Paclitaxel = CP, Carboplatin = P.

as well as with development of grade 3 or higher toxicity. In addition, in patients receiving CP, there was an association between IADL and OS. Hence, it may be useful to assess IADLs when prescribing chemotherapy both in clinical practice and in trials. Our findings of significant association of other PROs like social activities and QOL with outcomes is similar to what has been found by other investigators [14,15].

The protocol allowed physician and patient choice of regimen and flexibility of dosing. The majority of the frailer patients eventually completed 4 cycles of chemotherapy, and, importantly, improvement in QOL with chemotherapy was seen in both cohorts, likely reflecting the efficacy of platinum-based therapy in this disease. Prior research has shown that ovarian cancer patients' QOL (encompassing the social domain) is associated with OS [16].

Several studies of older patients with cancer have demonstrated that there is a relationship between results of a geriatric assessment, chemotherapy toxicity, subsequent functional decline, and

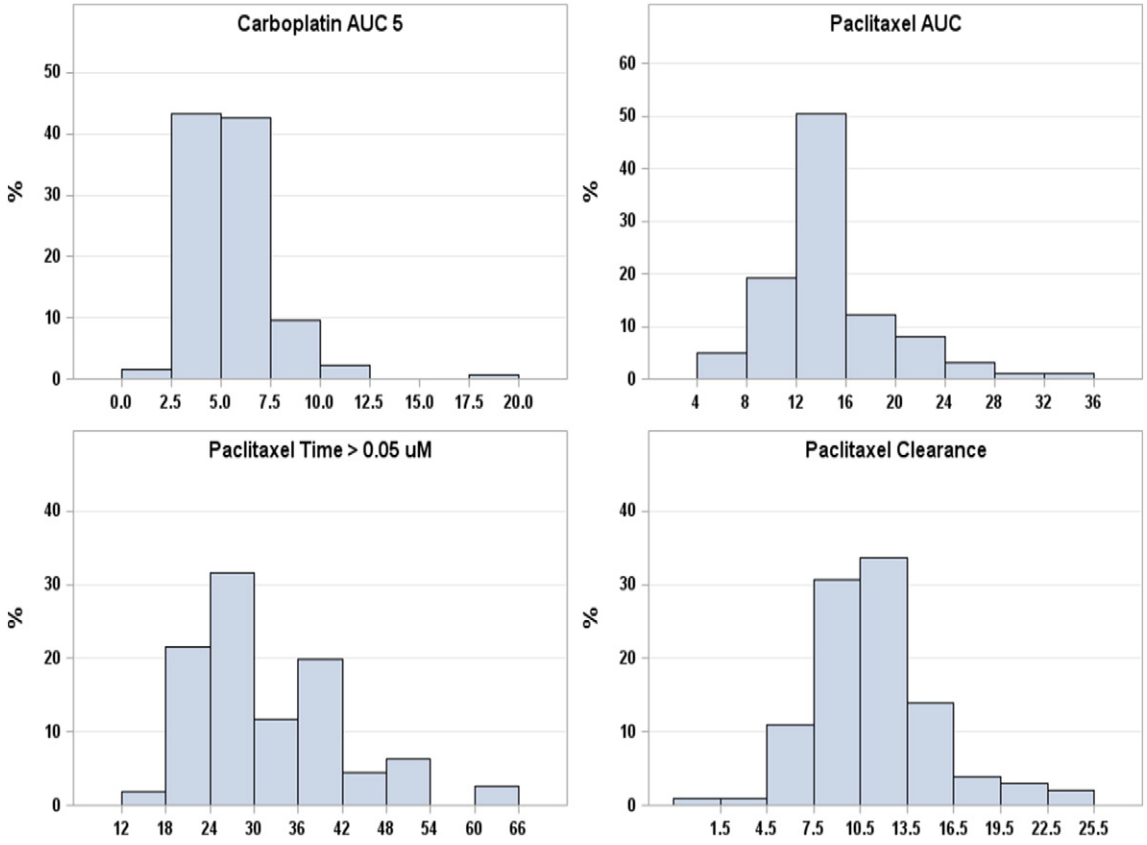

Fig. 6. Distribution of pharmacokinetic properties of carboplatin and paclitaxel. AUC = area under the curve.

OS [17–19]. However, only a few of these studies have been performed among patients with ovarian cancer [20]. In a study of carboplatin and cyclophosphamide, the GINECO group found that toxicity was associated with pre-treatment functional status and depression [21]. The GINECO group recently performed a pooled analysis on 3 phase II studies and found a correlation between overall survival and decreased functionality with the IADL tool [22]. In a second report, evaluating 2 sequential trials of carboplatin/cyclophosphamide and carboplatin/paclitaxel, older age, stage IV disease, use of paclitaxel and depression were associated with lower OS [23]. The importance of incorporating geriatric tools in clinical trials has been stressed by the IOM, ASCO, and the Cancer and Aging Research Group [24–28]. As demonstrated in this present study, PROs can aid in understanding the heterogeneity of the study population, choice of treatment, and risk factors for toxicity.

Debate continues in regards to relative benefits of treatment with primary chemotherapy versus primary surgery in women with ovarian cancer, however, it is clear that more primary chemotherapy is being used in the elderly population [29,30]. Less surgery is being performed in the oldest of old [31–33]. Patients receiving neoadjuvant chemotherapy do not always eventually receive surgical debulking [34]. In the CP cohort approximately 50% of patients received primary chemotherapy with 25% not having surgery while on trial. In the C arm, almost 60% had primary chemotherapy and over 50% of these did not receive surgery during the study.

The mean observed carboplatin AUC in the current study was close to the target value of AUC 5, while the variability around this value was quite large [35]. These results may be explained by our approach of estimating the AUC value from a single value of total platinum at 24 h [36,37]. The observed paclitaxel exposure of 14.8 ($\pm$4.8) μM * h is very similar to previously reported values of 13.1 ($\pm$4.4) μM * h at the same dose level [38]. The lack of an observed correlation between paclitaxel PK parameter values and neurotoxicity may be explained by the lower dose of 135 mg/m^2 compared to studies that did observe such a relationship [39].

A weakness of the study includes a non-randomized design. The GOG considered randomization, however, was very concerned with the ability to accrue patients and the potential for grade 3–4 toxicity. This was the first elderly-patient specific trial conducted by the GOG, therefore, much discussion was held in regarding the clinical trial approach. In addition, it was the group's first trial using a battery of PROs. We used PROs for IADLs, ADL, social activities and QOL.

Identifying populations with decreased tolerance to chemotherapy should allow appropriate starting dose reductions and design of interventions to decrease toxicity in these frailer groups. IADL is a very easily administered tool that should be useful for this purpose.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2016.11.033.

Conflicts of interest

Dr. Jan Beumer receives grant monies from MCI as well as support for travel to meetings for the study or other purposes.

Dr. Thomas Herzog is on the Advisory Board for AstraZeneca, Roche and Johnson and Johnson.

Dr. Arti Hurria serves as a board member for ASCO Board of Directors as well as SIOG Board. Dr. Hurria receives compensation for board membership from ASCO Cancer.net Editorial Board and JGO Editorial Board. He also receives monies for consultancy services from Boehringer Ingelheim Pharmaceuticals, Carevive, Sanofi, and GTx, Inc. Dr. Hurria's institute receives researching funding from Celegene, Novartis and GSK.

Dr. Robert Higgins receives grant monies from Carolinas Medical Center.

Dr. Angeles Alvarez Secord received personal fees for serving on the advisory board for Janssen, Clovis Oncology, Genentech, and AstraZeneca. She also received grant funding from Genentech, Amgen, Endocyte and Exelixis. Dr. Secord received grant money and personal fees for serving on an advisory board at Astex Pharmaceuticals, Inc., and Boerhinger Ingelheim. Dr. secord received grant funding from Prima Biomed, Tesaro, Eisai Morphotek, Bristol Myers Squibb and Incyte. She received personal fees from Glasko Smith Klein and Precision Therapeutics while serving on an advisory board, and also received grant money from Abbie-Vie.

All other co-authors have no conflicts of interest to report.

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Original Research

Multidisciplinary development of the Geriatric Core Dataset for clinical research in older patients with cancer: A French initiative with international survey

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KEYWORDS
Clinical trials;
Data set;

Abstract ***Background:*** To define a core set of geriatric data to be methodically collected in clinical cancer trials of older adults, enabling comparison across trials.
Patients and methods: Following a consensus approach, a panel of 14 geriatricians from oncology clinics identified seven domains of importance in geriatric assessment. Based on

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Delphi consensus;
Geriatric assessment;
Cancer;
Older patients

the international recommendations, geriatricians selected the mostly commonly used tools/items for geriatric assessment by domain (January–October 2015). The Geriatric Core Dataset (G-CODE) was progressively developed according to RAND appropriateness ratings and feedback during three successive Delphi rounds (July–September 2016). The face validity of the G-CODE was assessed with two large panels of health professionals (55 national and 42 international experts) involved both in clinical practice and cancer trials (March–September 2017).

Results and discussion: After the last Delphi round, the tools/items proposed for the G-CODE were the following: (1) social assessment: living alone or support requested to stay at home; (2) functional autonomy: Activities of Daily Living (ADL) questionnaire and short instrumental ADL questionnaire; (3) mobility: Timed Up and Go test; (4) nutrition: weight loss during the past 6 months and body mass index; (5) cognition: Mini-Cog test; (6) mood: mini-Geriatric Depression Scale and (7) comorbidity: updated Charlson Comorbidity Index. More than 70% of national experts (42 from 20 cities) and international experts (31 from 13 countries) participated. National and international surveys showed good acceptability of the G-CODE. Specific points discussed included age-year cut-off, threshold of each tool/item and information about social support, but no additional item was proposed.

Conclusion: We achieved formal consensus on a set of geriatric data to be collected in cancer trials of older patients. The dissemination and prospective use of the G-CODE is needed to assess its utility.

1. Introduction

Although cancer is prevalent in the older segment of the population, older adults with cancer remain underrepresented in cancer clinical trials that establish new standards of care [1]. As a result, we lack robust data on the benefit/risk balance for many treatment strategies in these patients.

Ageing is a heterogeneous process that stresses the clinical need to identify comorbid conditions and ageing-related physiologic changes, both well-known factors increasing the risk of treatment side-effects and poor outcomes [2].

Geriatric assessment (GA) is defined by geriatricians as a multidimensional interdisciplinary assessment of the general health status of the older patient, reviewing the medical, psychosocial, functional and environmental domains. For each domain, several tools are available, but consensus is lacking on which tool to use and the optimal cut-offs or threshold scores [3,4]. The literature supports the prognostic value of the GA and its utility in weighing the benefits and risks of cancer treatments in older adults [5–8]. However, GA has not been implemented in routine oncology practice or in cancer clinical trials.

In 2011, after a workshop on clinical trial methodology in older adults with cancer, the Elderly Task Force of the European Organization for Research and Treatment of Cancer (EORTC) recommended the use of a standardised minimum data set (minDS) for assessing the global health and functional status of older populations [9]. This minDS consisted of the G8 screening tool [10], the Instrumental Activities of Daily Living (IADL) questionnaire [11], the Charlson Comorbidity Index [12] and data on social situation. The approach and the scientific method used to define the minDS were not clearly explained, and the appropriation of the minDS for target users was not studied.

The DIalog for personALization of management in geriatric OncoloGy (DIALOG) intergroup was launched in 2014, bringing together the network of the Société Francophone d'OncoGériatrie (SoFOG, or French society of geriatric oncology) and the Unicancer cooperative group GERICO dedicated to clinical research in geriatric oncology. One of its first actions was to address the update of the EORTC initiative, with the goal to describe more accurately the population of older adults (70 years) with cancer and to standardise geriatric data collection in clinical trials in a brief and practical way. The proposed project, named Geriatric Core Dataset (G-CODE), implied the use of tools/items validated in older cancer and non-cancer populations that covered the main domains of the GA. In addition, the collection of data was to be feasible at baseline in the curative or palliative setting, regardless of the tumour type. For this purpose, DIALOG appointed a taskforce including geriatricians and oncologists to develop the G-CODE following an explicit consensus approach.

2. Method

2.1. Study design and general process

The process was divided into successive steps (Fig. 1) and with four groups of experts (Supplementary Data S1): (a) elaboration of the initial set of selected tools/

items (committee 1, part 1); individual scoring (by email) of the relevance and appropriateness of the tools/items in three rounds (committee 1, part 2) [13]; (b) reporting to the steering committee (SC) the results from the scoring committee (committee 1); (c) assessment of the face validity of the G-CODE (i.e. the extent to which the G-CODE is subjectively viewed as covering the concept it purports to measure) by two panels of national experts (n = 55, committee 2) and international experts (n = 42, committee 3) including oncologists, geriatricians, clinical research associates and nurses.

No ethical approval was required to conduct this research.

The SC supervised the research (Delphi consensus method, national and international survey), identified and appointed experts to the committees and analysed the results. The SC included four oncologists (P.S., C.T., E.B., L.M.), one public health specialist (SMP) and three geriatricians (E.P., P.C., T.C.).

2.2. Development of the initial geriatric core data set (committee 1, part 1)

All 14 members of committee 1 agreed to include tools/items exploring the following seven domains of GA: social environment, functional status, mobility, nutritional status, cognitive status, mood and comorbidities. Working in pairs, they selected one domain to investigate. From recommendations on GA developed by the International Society of Geriatric Oncology (SIOG) [3], EORTC [4] and National Comprehensive Cancer Network [14], the geriatrician pairs had to list the available tools/items by domain, determine the most commonly used, search studies assessing the sensitivity and specificity of each and assess tools/items from a practical standpoint. Tools/items could be validated for use in older patients with or without cancer. They had to be brief and practical for widespread use. Then committee 1 members attended an in-person meeting at the annual SoFOG conference (October 7–9, 2015; Toulouse, France). Each geriatrician pair presented its recommendations of tools/items and the reasons for supporting their choices to include in the assessment. These initial sets were then shared and discussed with the SC in a plenary meeting (October 29, 2015, Paris), while the Delphi consensus methodology was explained.

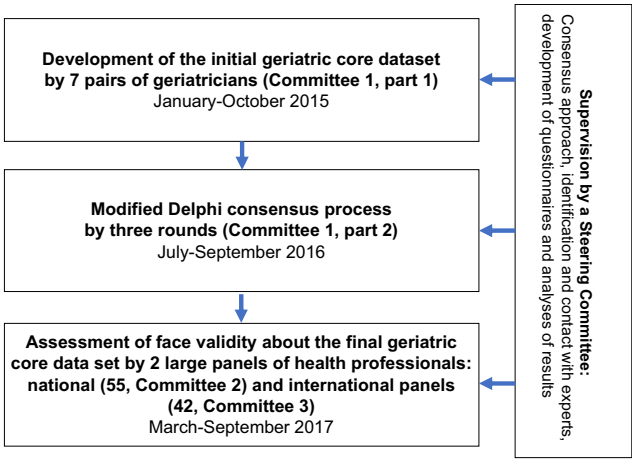

Fig. 1. Main steps of development of the geriatric core data set in cancer clinical research for older patients.

2.3. Modified Delphi consensus (committee 1, part 2)

Committee 1 members agreed on tools/items to be selected in a three-round Delphi method. Rules for scoring and analysis of the scores were defined *a priori*. The first set of tools/items was sent by email to each member of the committee for individual rating. For each tool/item, experts were asked to indicate, on a scale ranging from 1 (totally disagree) to 9 (totally agree), the degree to which the specific tool was relevant to assess the investigated domain.

After each round, only tools/items with strong consensus (rating score range 7–9) were included for consideration in the G-CODE, with all others being tested in a new questionnaire. Therefore, questionnaires were drafted for further rounds with only tools/items lacking strong consensus before being sent to each member of committee 1 with the results of previous round(s) and a copy of their previous scores. Scales and rating methodology were identical across the successive rounds.

To reach a final proposition for the G-CODE, the SC held an in-person meeting to discuss the results after each round.

2.4. Face validity of the G-CODE assessed by national and international panels (committees 2 and 3)

The SC developed a questionnaire adapted from the Appraisal of Guidelines for Research and Evaluation II Instrument [15] with eight questions in five sections (Supplementary Data S2: scope and purpose, stakeholder involvement, accuracy of development, clarity of presentation and applicability). Experts completed an online survey [16] and rated each of the eight questions from 1 (totally disagree) to 7 (totally agree); they could provide additional comments (open text).

2.5. Pilot study of the G-CODE administration

The time to complete the G-CODE final version was measured in three university hospitals with 50 consecutive cancer older patients. The full questionnaire was administrated by a geriatrician, an oncologist or a nurse.

2.6. Data analyses

The 14-member committee 1 is described by the practice location and experience (senior 10 years). National and international panels are described by country and

specialty. Each round of the Delphi method with consensus level is reported. We report results from the national and international panels for each question, including the median and minimum and maximum scores as well as the proportion of disagreement, defined as the proportion of scores ranging from 1 to 3. Finally, from the pilot study, we report the median, range and interquartile range for the administration of the G-CODE by health professionals.

3. Results

3.1. Development of the initial geriatric core data set

Expert geriatricians represented 11 different French geriatrician teams involved in oncology, and 12 (85%) had a senior clinical practice in geriatrics (Supplementary Data S1). The initial data set was derived for seven domains (Table 1): social environment, functional status, mobility, nutritional status, cognitive status, mood and comorbidities. The list of available tools/items by geriatric domain was discussed in a plenary meeting (October 29, 2015) and is presented in Supplementary Table S1. For each domain, one pair of geriatricians selected a tool/item based on its brevity and ability to be administered in the cooperative group setting. However, for a given geriatric domain, we could not compare the diagnostic accuracy of the available tools/items given the lack of data in the literature.

3.2. Delphi process

After sharing results of the selection of the initial geriatric core data set, all 14 geriatricians from committee 1 went through the Delphi process. In the first round, the questionnaire included 15 tools/items. Results showed strong consensus for two tools: Activities of Daily Living (ADL) and short-IADL (4-IADL). Other tools/items were included in the second round, which led to strong consensus for 10 tools (Table 2). After the third round, 12 tools/items were selected for presentation to the SC. To keep the instrument short and user-friendly, all SC members agreed to limit the selection to one tool/item per domain, ruling out 'gait speed' and the Mini Nutritional Assessment-Short Form. For the cognitive status, the Mini-Cog was selected.

Table 1
Tools/items identified as relevant by the geriatrician experts.

Geriatric domains	Selected tools/items for scoring
Social status	- Do you live alone? - Do you live in nursing home? - Do you have a person or caregiver to help you?
Functional status	- Katz Activity of Daily Living (ADL) index (6 items) - Lawton Instrumental ADL score (4 items)
Mobility	- Timed Up and Go test - Gait speed
Nutritional status	- Weight loss during the last 6 months > 10% - Body mass index - Mini Nutritional Assessment
Depression	- Mini-Geriatric Depression Scale (4 items)
Cognition	- The 5-word test - Clock drawing test - Mini-Cog (3 items)
Comorbidity	- Updated Charlson Comorbidity Index (12 items)

Finally, seven domains and ten tools/items were retained in the G-CODE final version: (1) 'Do you live alone?' AND 'do you have a person or caregiver able to provide care and support?'; (2) ADL [17] and 4-IADL [18]; (3) Timed Up and Go test (TUG) [19]; (4) weight loss during the past 6 months and body mass index (BMI); (5) Mini-Cog [20]; (6) mini-Geriatric Depression Scale (mini-GDS) [21] and (7) Charlson Comorbidity Index [22].

Face validity of the geriatric core data was assessed by the national and international panels (Supplementary Data 1 and 2).

Of 55 members in the national panel, 42 (76%) completed the survey. Members lived in 20 cities within France. Among the 42 members of the international panel, 31 (74%) completed the survey. Members were from 13 countries.

None of the panel members suggested including additional items. All questions (Table 3) were scored 4–7 by 95% of the national panellists; only the question of the composition of the validation group (16.7%) was scored 1–3 by 16.7% of the members. Most members of the international panel (90%) rated all questions with 4–7 scores. In free comments (Supplementary Table S2), the participants asked for additional clarification and/or more information on the research context, the definition of 'old age' (70 year) and the composition of panels and disciplines represented.

The final G-CODE with the user guide is presented in Supplementary Data S3. We administered the G-CODE to a sample of 50 older patients (median age 81 years, range 70–97), with stage I to IV breast (36%), GI (18%), gynaecologic (14%), genitourinary (12%), lung (10%), head and neck (4%) or other (6%) cancer. The median completion time was 8.05 min (interquartile range 6.22–9.07).

4. Discussion

The goal of the G-CODE project was to define a minimum set of geriatric data to be collected in cancer clinical trials that would allow for both a minimal geriatric description of the older patients with cancer and standardisation of geriatric data. An essential

Table 2
Tool/item assessment and selection by round in the Delphi consensus and final Geriatric Core Dataset (G-CODE).

Delphi rounds	Appropriate with strong consensus[a]	Appropriate with relative consensus	Uncertain
Round 1			
	ADL, 4-IADL	Other items	The 5-word test 'Do you live in nursing home?' Y/N
Round 2			
	Mini-Cog Mini-GDS UpCCI MNA-SF, BMI, weight loss TUG, GS 'Do you live alone?' 'Do you have a person or caregiver to help you?'	The 5-word test Clock drawing test	'Do you live in nursing home?'
Round 3			
			'Do you live in nursing home?' The 5-word test Clock drawing test
Final G-CODE with 10 tools[b]	ADL and 4-IADL Mini-Cog Mini-GDS UpCCI BMI and weight loss TUG 'Do you live alone?' Y/N 'Do you have a person or caregiver to help you?' Y/N		

ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; Mini-GDS, mini-Geriatric Depressive Scale; UpCCI, updated Charlson Comorbidity Index; MNA-SF, Mini Nutritional Assessment-Short Form; BMI, body mass index; TUG, Timed Up and Go; GS, gait speed.

[a] Each tool was defined as appropriate, (i.e. relevant and to be included in the core data set) if the median of all scores was 7 with strong (rating score range 7–9) or relative (5–9) consensus among all members; inappropriate (i.e. not to be included in the G-CODE) if the median of all scores was <3.5, with strong (rating score range 1–3) or relative (1–5) consensus and uncertain if the median of all scores was 4–6.5 or with absence of consensus.

[b] Exclusion by the steering group of redundant tools in the same domain after round 3: GS for mobility and MNA-SF for the nutritional status.

prerequisite was to develop a tool that would be user-friendly for any professional involved in cancer care for older patients, so as to be easily implemented in any clinical trial for any tumour type at study entry and at follow-up. The G-CODE was developed after a multi-stage modified Delphi consensus method with individual ratings of appropriateness. Consensus resulted in the selection of two social questions, two autonomy scales (ADL and 4-IADL), one mobility scale (TUG), two nutrition items (weight loss and BMI), one cognitive scale (Mini-Cog), one scale assessing the mood (mini-GDS) and one comorbidity overview (updated Charlson Comorbidity Index). The face validity of this selection was checked with one national and one international multidisciplinary panel, which besides cancer specialists also included clinical research associates and nurses.

The inclusion of the G-CODE in clinical trials will provide a clearer description of the characteristics of older patients enrolled in clinical trials, with a better chance to interpret the application of results to standard practice. Moreover, it will allow for comparing and merging data from different studies.

Several researchers have developed brief GA instruments or comprehensive GA to help oncologists select patients for cancer strategies, including self-administered tools [23–26] and frailty screening tools [10,27,28]. Except for the two tools [9,25], none was devised for research purposes to provide comprehensive information on the overall health status of older patients at baseline when enrolled in a clinical trial. The tool developed by Hurria *et al.* [25] (CALGB) has 75 items and a median completion time of 22 min. It is primarily self-administered by the patient, and only a small part requires a healthcare provider. Although CALGB has been found feasible in the US trials [26], European cooperative groups are often reluctant to propose it widely in trials of older patients. Although cognitive and mood domains have predictive and prognostic value for mortality, toxicity and functional decline in older patients with cancer [29–31], these are not accounted for in the EORTC minDS [9].

Recently, the published ASCO Guidelines for GA established a minimum GA for clinical practice in older patients undergoing chemotherapy [32], including IADL to assess function, a thorough history or validated tool to assess comorbidity, a single question for falls, the GDS to screen for depression, the Mini-Cog or the Blessed Orientation-Memory-Concentration test to screen for cognitive impairment and an assessment of unintentional weight loss to evaluate nutrition. Except

Table 3
Results of scores by questions (face validity survey of the G-CODE) from the national and international panel survey (score 1 [totally disagree] to 7 [totally agree]).

	1. Objectives are clearly explained	2. The patient population addressed is clearly defined	3. Validation group represents all professionals concerned with its use	4. The target users	5. The approach and the scientific method used	6. The items are precise and unambiguous	7. Advice is provided for the use	8. All the questions can be easily completed
National panel (n = 42)								
Min	1	1	1	1	4	4	1	1
Max	7	7	7	7	7	7	7	7
Median	6	7	5	6	6	7	6	6
% score 1–3	2%	5%	16.7%	5%	0%	0%	5%	5%
International panel (n = 31)								
Min	2	3	3	2	4	2	2	3
Max	7	7	7	7	7	7	7	7
Median	6	6	6	6	6	6	6	6
% score 1–3	6.5%	6.5%	6.5%	6.5%	0%	3.2%	9.7%	3.2%

G-CODE, Geriatric Core Dataset.

for the single question for falls and the longer version of GDS, the proposed tools are identical to those of the G-CODE.

To the best of our knowledge, no such set of geriatric data to be collected has been proposed based on a rigorous development method (e.g. Delphi consensus process) and a formalised international validation process.

Various specific points were discussed in the face validity step. First, the 70-year age cut-off was debated. Indeed, 65 years is often used as a threshold age for performing a GA in international studies. We preferred to recommend the G-CODE for patients 70 years because this is the age threshold chosen by the EORTC [4] and SIOG [33] and is being used more often in recent clinical trials. Second, some tools/items selected for the final version (mini-GDS, TUG, BMI) have thresholds. Given the descriptive essence of the G-CODE, we decided to remove these thresholds. Third, some tools/items were debated: social questions (Are they precise and unambiguous?), 4-GDS (Is it efficient to detect depression?) and 4-IADL (Is it validated in oncology?). For social questions, all participants eventually agreed on the essential information for available social support not covered by any short tool [3], and we provided instructions on how to complete these two questions (Supplemental S3). Depression is commonly found in patients with cancer, as a preexisting condition or as a result of illness and treatment [34]. Short screening tools or self-reported questionnaires have shown limited accuracy to diagnose depression [35]. The main purpose of the G-CODE was to provide descriptive and quantitative information about enrolled patients, and hence, the GDS-4 achieved consensus as a fast yet effective screening test. The 4-IADL questionnaire evaluates advanced self-care activities (ability to use a telephone, take medications, manage finances and use transportation). We decided to keep the 4-IADL questionnaire because of its brevity and its association with poor survival in haematological malignancies [36]. Finally, one expert questioned the inclusion of performance tests (i.e. TUG and Mini-Cog) because they cannot be administered in all circumstances. However, because the G-CODE aimed at describing all geriatric domains, mobility and cognition had to be included and quantified.

Limitations to this study include the lack of international geriatricians in the first committee (development of the initial core data set), which may limit the wide dissemination and international use of the G-CODE. However, the face validity, assessed by the two large panels of national and international health professionals, highlights its good acceptability. Moreover, neither of the two panels suggested additional items.

5. Conclusion

This is the first report of a Delphi method to establish a minimum geriatric data set for cancer research purposes. Here, we propose a simple instrument based on validated tools for older patients, allowing for a standardised description of these patients with cancer when enrolled in specific or non-specific clinical trials.

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Conflict of interest statement

The authors have declared no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2018.07.137.

Appendix B

Collaborators of G-CODE project:

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A Phase II Trial of Older Adults With Metastatic Breast Cancer Receiving *nab*-Paclitaxel: Melding the Fields of Geriatrics and Oncology

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Abstract

***nab*-Paclitaxel may be an attractive therapy for older adults because of its efficacy, the infrequency of allergic reactions, and the lack of need for steroid pre-medications. We evaluated the tolerability and efficacy of *nab*-paclitaxel in older adults with metastatic breast cancer, as well as the relationship between a geriatric assessment-based toxicity risk score and chemotherapy toxicity, dose reductions, dose delays, and hospitalizations. Patients with intermediate/high toxicity risk scores had higher risk of grade ≥ 3 toxicity than those with low risk scores, and a higher mean risk score was associated with higher likelihood of dose reductions and hospitalizations. A geriatric assessment-based risk score can help weigh the risks and benefits of chemotherapy in older adults, and should be incorporated into future trials testing new therapies in this population.**

Introduction: Phase II clinical trials including geriatric assessment (GA) measures are critical for improving the evidence base for older adults with cancer. We assessed the efficacy and tolerability of *nab*-paclitaxel in older adults with metastatic breast cancer (MBC). **Patients and Methods:** Patients aged 65 years with MBC and 1 previous line of chemotherapy received 100 mg of *nab*-paclitaxel on days 1, 8, and 15 of a 28-day cycle. A GA was completed pre-chemotherapy, and the validated Cancer and Aging Research Group (CARG) chemotherapy toxicity risk score was calculated. Relationships between tolerability (number of courses, hospitalizations, dose reductions, and toxicity) and risk score were assessed using general linear models, Student *t* tests, and the Fisher test. Response rate and progression-free survival were evaluated using the Kaplan-Meier method. **Results:** Forty patients (mean age, 73 years; range, 65-87 years) were included. The median number of cycles was 6, 75% (n = 30) of patients had 1 dose hold, and 50% (n = 20) had 1 dose reduction. Fifty-eight percent (n = 23) had treatment-related grade 3 toxicities, and 30% (n = 12) were hospitalized owing to toxicity. Thirty-five percent (n = 14) responded, and the median progression-free survival was 6.5 months (95% confidence interval, 5.5 months to undefined). Patients with intermediate/high toxicity risk scores had higher risk of grade 3 toxicity than those with low risk scores (odds ratio, 5.8; 95% confidence interval, 1.3-33.1; $P = .01$). A higher mean risk score was associated with higher likelihood of dose reductions and hospitalizations. **Conclusions:** Among older adults with MBC receiving weekly *nab*-paclitaxel, more than one-half experienced grade 3 chemotherapy toxicity. However, a GA-based risk score could predict treatment tolerability.

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Introduction

Breast cancer is a disease associated with aging,[1] and almost one-half of breast cancer diagnoses occur in women age 65 and older.[2] However, older adults with breast cancer have been underrepresented in registration clinical trials that inform the recommended drug dosing and expected toxicity profiles, which is included within the package insert.[3,4] Furthermore, little is known about whether older adults included in clinical trials are representative of the general population, because geriatric assessment (GA) measures are not included.[5] In order to improve the evidence base for treatment of older adults with cancer, the Institute of Medicine, the American Society for Clinical Oncology, and the Cancer and Aging Research Group (CARG)[6] have identified phase II clinical trials including GA measures as a critical component to improve the evidence base for treating older adults with cancer.[7,8]

A recent systematic review identified only 16 phase II trials focusing on older patients treated with chemotherapy for metastatic breast cancer published between 2001 and 2014.[9] Yet most of these studies did not include geriatric-specific evaluations, and patients were enrolled based on chronologic age alone. Factors besides chronologic age may affect treatment tolerance in older patients, and a more detailed evaluation is warranted.[10] This evaluation is known as the GA, and it measures a patient's functional status, comorbidities, cognition, nutritional status, social support, and psychological state.[11] There is an abundance of information demonstrating that GA detects general health care problems in older patients with cancer that routinely are underrecognized in clinical oncology care.[12] Furthermore, in older patients with cancer, the GA has been shown to predict both survival[13-17] and severe chemotherapy toxicity.[18-22] The CARG chemotherapy toxicity calculator, which utilizes data from the GA, was developed and validated in 750 older adults with solid tumors receiving chemotherapy, and has been shown to predict grade 3-5 chemotherapy toxicity more accurately than currently used measures such as the Karnofsky performance status.[18,19]

Current guidelines list weekly taxanes among the preferred options for treating older adults with metastatic breast cancer.[23] Nanoparticle albumin-bound (*nab*) paclitaxel has proven to be an efficacious and safe alternative to solvent-based taxanes (such as paclitaxel and docetaxel), because it requires no premedication and has a lower rate of hypersensitivity reactions.[24] Although retrospective studies have shown that *nab*-paclitaxel appears to be safe in older adults,[25] its clinical benefit and tolerability have not been prospectively assessed.

In this study, we evaluated the efficacy and the tolerability of weekly *nab*-paclitaxel in older adults with metastatic breast cancer. Furthermore, we explored the use of a previously developed and validated GA-based risk score (CARG Chemotherapy Toxicity Calculator)[18,19] to predict the need for dose reductions, dose delays, hospitalizations, and/or grade 3 to 5 chemotherapy toxicity attributed to treatment.

Materials and Methods

Study Design and Objectives

This was a phase II, single-arm, open-label, clinical trial of *nab*-paclitaxel in older adults with metastatic breast cancer conducted at City of Hope National Medical Center in Duarte, CA and Ohio State University Cancer Center in Columbus, OH. The primary objective was to assess tolerability, defined as the presence of grade 2 to 5 chemotherapy toxicity, and dose reductions, delays, or interruptions. Secondary objective included estimation of overall response rate (ORR, defined as the sum of complete and partial response), median progression-free survival [PFS], median overall survival (OS), the use of a cancer-specific GA to describe the study population, and the CARG chemotherapy toxicity calculator to predict the need for dose reduction, dose delays, or occurrence of grade 3 to 5 chemotherapy toxicity. This study was approved by the City of Hope National Medical Center Institutional Review Board and all study participants provided written informed consent. The study was registered at clinicaltrials.gov (NCT01463072).

Eligibility

Patients were eligible if they were age 65 years, had a diagnosis of metastatic breast cancer with any hormone receptor or human epidermal growth factor receptor 2 status, and were able to provide informed consent. Patients with 0 to 1 previous lines of chemotherapy for metastatic disease were eligible. Additional inclusion criteria were: Karnofsky Performance Status score 70%; resolution of grade 2 toxicity from prior therapy (other than alopecia); peripheral neuropathy grade 1; neutrophil count 1500/mm^3; platelets 100,000 cells/mm^3; hemoglobin 9.0 g/dL; and adequate hepatic and renal function. Patients were excluded if they were receiving any other investigational agents; had untreated or symptomatic central nervous system metastases; had a known allergy to paclitaxel; had received a taxane for adjuvant therapy or metastatic disease in the last 12 months; or had any serious uncontrolled infection.

Treatment Plan

Baseline evaluations included a complete medical history and physical examination. Blood was obtained for complete blood cell counts and metabolic panels. A contrast-enhanced computed tomography scan of the chest, abdomen, and pelvis was conducted prior to treatment initiation.

nab-Paclitaxel was administered on an outpatient basis at a dose of 100 mg/m^2 intravenously on days 1, 8, and 15 of a 28-day cycle. Patients were followed for adverse events throughout the study period, and these were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[26] Hospitalizations related to chemotherapy-related toxicity were recorded.

Drug delays were allowed for patients with grade 2 neutropenia, platelet count $< 100{,}000/mm^3$, and hemoglobin 9.0g/dL. *nab*-Paclitaxel was held in cases of grade 2 to 3 peripheral neuropathy and restarted at a dose of 80 mg/m^2 after neuropathy became grade 1. Patients with other grade 3 toxicities, as well as those with grade 1 to 2 toxicities deemed significant by the treating physician, could also have a dose delay or reduction at physician discretion.

Response Assessment

Computed tomography scans of the chest, abdomen, and pelvis were performed every 2 cycles or sooner if clinically indicated.

Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[27]

GA and Chemotherapy Toxicity Risk Score

A GA was completed prior to study initiation, prior to the third cycle of therapy, and at study termination. This tool[28,29] included an evaluation of functional status (Activities of Daily Living[30] and Instrumental Activities of Daily Living [IADL])[31]; physical function (Timed Up and Go test,[32] number of falls,[33] comorbidities [Older Americans Resources and Service comorbidity scale])[34]; number of medications; cognition (Blessed Orientation-Memory-Concentration test)[35]; psychological state (Mental Health Inventory-17)[30]; social support (Medical Outcomes Study Social Support survey)[30]; social functioning (Medical Outcomes Study Social Activity Limitations Measure)[30]; and nutritional status (body mass index and self-reported weight loss).

The CARG chemotherapy toxicity risk score was calculated for each patient at baseline prior to the first cycle of *nab*-paclitaxel.[18,19] The variables included in the prediction model and scoring algorithms, as well as risk of toxicity by score, are shown in Figure 1. Patients were categorized as being at low, intermediate, or high risk of chemotherapy toxicity according to their risk score.

Statistical Analysis

Rates and associated 95% confidence limits were estimated for: (1) grade 2 chemotherapy toxicity; (2) dose reductions, delays, and holds; (3) hospitalizations; and (4) ORR. Median PFS and OS were estimated using the method of Kaplan and Meier. Descriptive statistics for patient demographics, number of cycles received, tumor characteristics, and geriatric assessment results are provided.

The baseline chemotherapy toxicity risk (represented by the rate of chemotherapy toxicity risk) was skewed to the right, indicating a log transformation, so we used a $\log_2$ transformation in order to analyze changes based on doubling of the rate of toxicity risk. We compared the $\log_2$ toxicity risk for participants who had at least 1 dose reduction, dose hold, or hospitalization to those that did not using a 2-tailed, 2-sample Student *t* test assuming unequal variances. The Fisher's exact test was used to compare the rates of grade 3 and above toxicities across CARG toxicity risk categories, and linear regression was used to determine if the toxicity risk predicted the number of courses completed.

Results

Patient Characteristics

Forty patients (mean age, 73 years; range, 65-87 years) were enrolled between June 2012 and January 2016. Thirty-eight (95%) enrolled at City of Hope and 2 (5%) at Ohio State. Table 1 displays the baseline characteristics and geriatric assessment results of the study patients. Forty percent (n = 16) were 75 years of age. Most participants were female (95%; n = 38), white (73%; n = 29), and non-Hispanic (83%; n = 33). Seventy-five percent (n = 30) had hormone receptor-positive tumors. Fifty-eight percent (n = 23) received *nab*-paclitaxel as their first line of chemotherapy for metastatic disease.

Tolerability

The median number of completed cycles was 6 (range, 0-33). Seventy-five percent (n = 30; 95% confidence interval [CI], 59%-87%) had 1 dose hold and 50% (n = 20; 95% CI, 34%-66%) had 1 dose reduction. Ten percent of participants (n = 4; 95% CI, 3%-24%) experienced delays in 1 cycle.

Ninety percent (n = 36; 95% CI, 76%-97%) had grade 2 or above toxicities that were attributable to treatment. Fifty-eight percent (n = 23) had grade 3 or above toxicities that were attributable to treatment. Only 1 participant had a grade 4 toxic event.

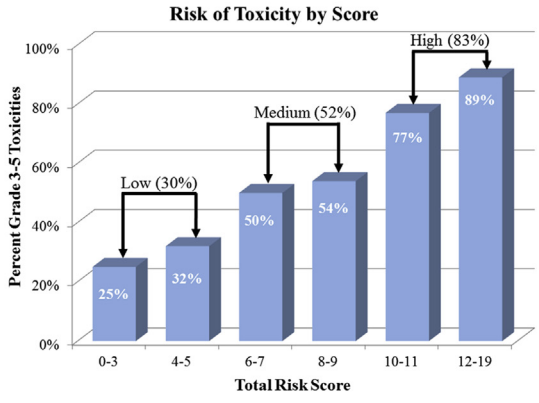
Figure 1 A, Prediction Model and Scoring Algorithm for Chemotherapy Toxicity; B, Percent Risk of Toxicity by Score

A

Variable	Value/Response	Score
Age of patient	≥ 72 years	2
	<72 years	0
Cancer type	GI or GU cancer	2
	Other cancer types	0
Planned chemotherapy dose	Standard dose	2
	Dose reduced upfront	0
Planned no. of chemotherapy drugs	Polychemotherapy	3
	Monochemotherapy	0
Hemoglobin	<11g/dL (male), <10g/dL (female)	3
	≥11g/dL (male), ≥10g/dL (female)	0
Creatinine clearance (Jeliffe ideal weight)	<34 mL/min	3
	≥34 mL/min	0
How is your hearing (with a hearing aid, if needed)?	Fair, poor, or totally deaf	2
	Excellent or good	0
No. of falls in the past 6 months	≥1	3
	None	0
Can you take your own medicine?	With some help/unable	1
	Without help	0
Does your health limit you in walking one block?	Somewhat limited/limited a lot	2
	Limited none of the time or a little of the time	0
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	Limited some of the time, most of the time, or all of the time	1
	Limited none of the time or a little of the time	0

See Hurria et al., *J Clin Oncol*, 2011; Abbreviation: GI, gastrointestinal; GU, genitourinary.

B



Abbreviations: GI = gastrointestinal; GU = genitourinary.

Table 1 Patient Demographic and Geriatric Assessment Results

Characteristic	Total (N = 40)	
	N	%
Age, y		
65-69	15	38
70-74	9	23
75	16	40
Gender		
Male	2	5
Female	38	95
Race		
Asian	6	15
Black	4	10
Caucasian	29	73
Other	1	3
Receptor status		
HR-positive	30	75
Triple-negative	10	25
Treatment line		
First line	23	58
Second line	17	43
IADL		
Median (range)	13	6-14
Dependence in at least 1 IADL	24	60
ADL (0-100)		
Mean (SD)	53.7	27.94
Dependence in ADL	26	65
1 fall in the previous 6 months	9	22.5
6% weight loss in the previous 6 months	10	25
Comorbidities		
Median (range)	3	0-6
Abnormal cognitive screening	3	7.5
Mental Health Inventory (0-100)		
Median (SD)	74.1	16.51
Social Support Survey (0-100)		
Mean (SD)	82.7	18.11
Hemoglobin level, g/dL		
Mean (SD)	11.8	1.61
< 11 (male), < 10 (female)	6	15
Creatinine clearance < 34 mL/min (Jeliffe)	3	7.5

Abbreviations: ADL = activities of daily living; HR = hormone receptor; IADL = instrumental activities of daily living; SD = standard deviation.

Ten percent (n = 4) experienced grade 2 peripheral sensory neuropathy (grade 2, 5%; n = 2; grade 3, 5%; n = 2). Thirty percent of the patients (n = 12; 95% CI, 17%-47%) were hospitalized owing to chemotherapy toxicity during the study period, and 28% (n = 11; 95% CI, 15%-44%) stopped treatment owing to treatment-related toxicity. Table 2 summarizes the most commonly observed adverse events.

Thirty-five percent (n = 14) of the patients were responders (95% CI, 21%-52%), with 3% (n = 1) complete response and 33% (n = 13) partial response. Forty percent (n = 16) of the patients achieved stable disease; 10% (n = 4) had disease progression; and 15% (n = 6) came off of treatment before 2 cycles. The median PFS was 6.5 months, (95% CI, 5.5 months to undefined), and the median OS was 21.2 months (95% CI, 14.6 months to undefined).

GA and Chemotherapy Risk Score

The results of the GA prior to treatment are shown in Table 1. Sixty percent (n = 24) of the patients required assistance in at least 1 IADL. Twenty-three percent (n = 9) reported at least 1 fall in the previous 6 months, 25% had involuntary weight loss, and 3% had an abnormal cognitive screening. One-half of the patients had 3 comorbidities. The mean score on the Mental Health Inventory-17 questionnaire (scores, 0-100) was 74 (SD, 16.5), and 35% (n = 14) reported poor emotional support. Using the CARG chemotherapy toxicity risk score, 53% (n = 21) of the patients were categorized at low, 38% (n = 15) at intermediate, and 10% (n = 4) at high risk of grade 3 chemotherapy toxicity (Figure 2).

Chemotherapy Risk Score and Tolerability

Because only 4 patients were in the high-risk category using the chemotherapy toxicity risk calculator, high and intermediate risk categories were combined. Patients with an intermediate or high toxicity risk had a higher risk of grade 3 chemotherapy toxicities than those with a low toxicity risk (odds ratio, 5.8; 95% CI, 1.3-33.1; $P = .01$) (Figure 2). Patients who had a dose reduction owing to chemotherapy toxicity were found to have a significantly higher mean toxicity risk than those who did not required a dose reduction (ratio of the group means = 1.38; 95% CI, 1.04-1.80; $P = .02$) (Figure 3A).

Patients who were hospitalized owing to chemotherapy toxicity had a significantly higher mean toxicity risk than those who were not hospitalized (ratio of the group means = 1.5; 95% CI, 1.13-2.00; $P < .01$) (Figure 3B). The toxicity risk was a significant predictor of the number of completed courses. A doubling in rate of toxicity risk resulted in a reduction in the number of completed courses by 4.5 (SE = 1.4; $P < .01$) (Figure 4).

Discussion

Among older adults with metastatic breast cancer receiving weekly *nab*-paclitaxel, more than one-half experienced grade 3 or higher chemotherapy toxicity. However, a GA-based risk score was able to predict treatment tolerability, and patients with higher toxicity risk were more likely to experience grade 3 toxicity, to need dose reductions, to receive fewer treatment cycles, and to be hospitalized than those with lower risk scores.

Determining the best treatment strategy for an older patient with metastatic breast cancer is a difficult task for clinicians. Therapeutic decisions are often based on chronological age alone, and older patients are less likely to receive standard, evidence-based care.[36] One reason for this is the underrepresentation of older adults (particularly those who are vulnerable and/or frail) in therapeutic clinical trials.[6] Therefore, understanding the tolerability and efficacy of chemotherapy in older adults, including those who are vulnerable and/or frail, is one of the highest priorities in geriatric oncology.[8]

This study evaluated a widely used agent, *nab*-paclitaxel, in a population of older adults with a significant proportion of

Table 2 Toxicities Experienced

Adverse Event Category	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Non-hematologic toxicities[a]	18 (45)	14 (35)	0 (0)
Heart failure	0 (0)	1 (3)	0 (0)
Diarrhea	3 (8)	3 (8)	0 (0)
Mucositis oral	0 (0)	1 (3)	0 (0)
Nausea	1 (3)	3 (8)	0 (0)
Vomiting	0 (0)	4 (10)	0 (0)
Fatigue	20 (50)	2 (5)	0 (0)
Pain	2 (5)	0 (0)	0 (0)
Allergic reaction	3 (8)	0 (0)	0 (0)
Infections and infestations other, specify	2 (5)	0 (0)	0 (0)
Upper respiratory infection	6 (15)	1 (3)	0 (0)
Urinary tract infection	4 (10)	1 (3)	0 (0)
Nail infection	2 (5)	0 (0)	0 (0)
Alanine aminotransferase increased	0 (0)	1 (3)	0 (0)
Aspartate aminotransferase increased	0 (0)	2 (5)	0 (0)
Dehydration	4 (10)	2 (5)	0 (0)
Hypocalcemia	1 (3)	1 (3)	0 (0)
Hypokalemia	2 (5)	1 (3)	0 (0)
Hyponatremia	0 (0)	1 (3)	0 (0)
Muscle weakness upper limb	0 (0)	1 (3)	0 (0)
Encephalopathy	0 (0)	1 (3)	0 (0)
Peripheral sensory neuropathy	2 (5)	2 (5)	0 (0)
Stroke	0 (0)	1 (3)	0 (0)
Cough	2 (5)	0 (0)	0 (0)
Dyspnea	2 (5)	1 (3)	0 (0)
Hypoxia	1 (3)	1 (3)	0 (0)
Hypotension	3 (8)	0 (0)	0 (0)
Thromboembolic event	1 (3)	1 (3)	0 (0)
Hematologic toxicities[a]	18 (45)	12 (30)	1 (3)
Anemia	13 (33)	7 (18)	0 (0)
Lymphocyte count decreased	6 (15)	1 (3)	0 (0)
Neutrophil count decreased	13 (33)	3 (8)	1 (3)
White blood cell decreased	21 (53)	4 (10)	0 (0)

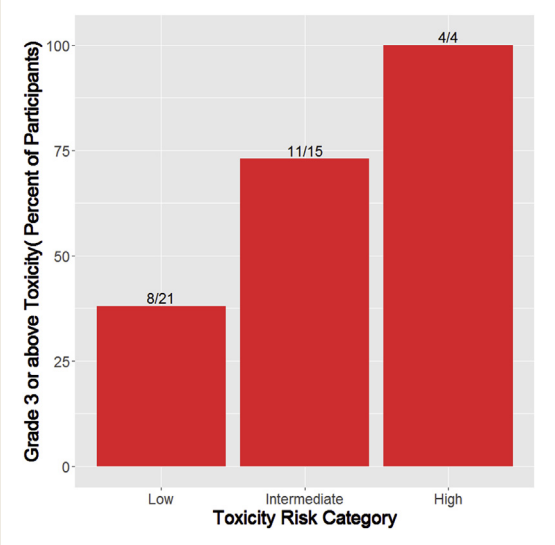
[a]Per Common Terminology Criteria for Adverse Events version 4.0; all Grade 3-4 toxicities or Grade 2 experienced by more than 1 participant.

functional deficits and comorbidities. *nab*-Paclitaxel could represent a less toxic alternative to solvent-based taxanes in vulnerable older patients owing to the lower incidence of allergic reactions and because no steroid premedication is needed.[24,25] Furthermore, we have previously demonstrated that pharmacodynamic variables of *nab*-paclitaxel are not influenced by chronological age.[37] In the randomized controlled trial (RCT) leading to approval of *nab*-paclitaxel, only 13% (n = 62) of the patients were older than 65,[38] and only 32 patients age 70 received *nab*-paclitaxel in a recently published RCT comparing various treatments among 799 patients with metastatic breast cancer.[39]

The proportion of patients with severe toxicity in our study was different than previously reported in a pooled analysis of patients older than 65 treated with *nab*-paclitaxel, with fewer cases of grade 3 neutropenia and sensory neuropathy in our cohort.[25] The lower incidence of neuropathy may be related to the very strict criteria for dose hold and dose reduction in our study compared with previous trials. *nab*-Paclitaxel was held in patients with grade 2 neuropathy and restarted at an 80% dose, whereas in previous trials, patients with grade 2 neuropathy have undergone dose reduction without dose holds.[39] In contrast, the ORR of 35% and the PFS of 6.5 months found in our study population were similar to those previously reported in a phase II trial utilizing a similar dosage of weekly *nab*-paclitaxel (45% and 7.5 months, respectively).[40] Of note, in that trial the mean age of the participants was 53.9 years, and only 17% were older than 65.

We have previously shown that a GA-based risk score can be used to predict severe chemotherapy toxicity in older patients across tumor types, and that the tool outperforms usual oncology assessments such as Karnofsky Performance Status.[18,19] In the present study, we evaluated the performance of our risk score to predict the tolerability of *nab*-paclitaxel in older patients with metastatic breast

Figure 2 Number of Participants With Grade 3 to 4 National Cancer Institute Common Terminology Criteria for Adverse Events by Cancer and Aging Research Group (CARG) Risk Category



cancer. Our results show that in this population, the risk score can identify patients who are at a high risk of experiencing severe toxicity or hospitalization, as well as those less likely to complete the planned treatment. Thus, this tool can potentially be integrated into RCTs in order to allocate patients to different treatment strategies, thus allowing for the enrollment of vulnerable and/or frail patients. A similar strategy was utilized in the recently published ESOGIA trial in lung cancer,[41] in which patients were assigned to different chemotherapy doses or supportive care depending on the results of a GA. This study showed that although GA-based treatment allocation for chemotherapy did not improve PFS or OS over usual care, it resulted in less all-grade toxicity (86% vs. 93%; $P = .015$), higher quality of life scores, and fewer treatment failures without compromising survival.[40,42]

This study has limitations. First, although we were able to show that the chemotherapy risk score predicted treatment tolerability, we cannot tell whether treatment modifications or dose reductions in patients with a high risk score will lead to less toxicity or different outcomes. However, this phase II trial sets the stage for RCTs comparing usual decision-making criteria (such as chronological age or simple performance status measures) to treatment allocation utilizing the chemotherapy toxicity risk score. Second, our patients were recruited at a comprehensive cancer center, and they may not be representative of patients seen in other settings. Nevertheless, it is important to emphasize that our cohort included a significant proportion of patients who had markers of vulnerability: 60% needed assistance in IADLs, 50% had 3 or more comorbidities, 40% had involuntary weight loss, and 23% had falls in the last 6 months. Third, although we were able to identify patients at higher risk of chemotherapy toxicity, we did not assess whether experiencing toxicity led to adverse functional outcomes or worse quality of life. Finally, most of our patients were non-Hispanic white, and thus the applicability of our results to other racial and ethnic groups with differing sociodemographic characteristics is limited.

Despite these limitations, our study has several strengths. It addresses a key research priority described by the Institute of Medicine, the American Society of Clinical Oncology, and the CARG by expanding the knowledge base regarding a commonly utilized chemotherapy agent in older adults with metastatic breast cancer. Furthermore, we showed that incorporating a GA and a

Figure 3 Association Between Toxicity Risk and Dose Reductions (A), and Hospitalizations (B). The Blue Dot Represents the Mean; Red Dots Represent Individual Participant Results. The Line Within the Box Represents the Median, the Upper and Lower Ends of the Boxes Represent the 25th and 75th Percentiles, and the Ends of the Whiskers Represent the Individual Result Within 1.5 Times the Interquartile Range

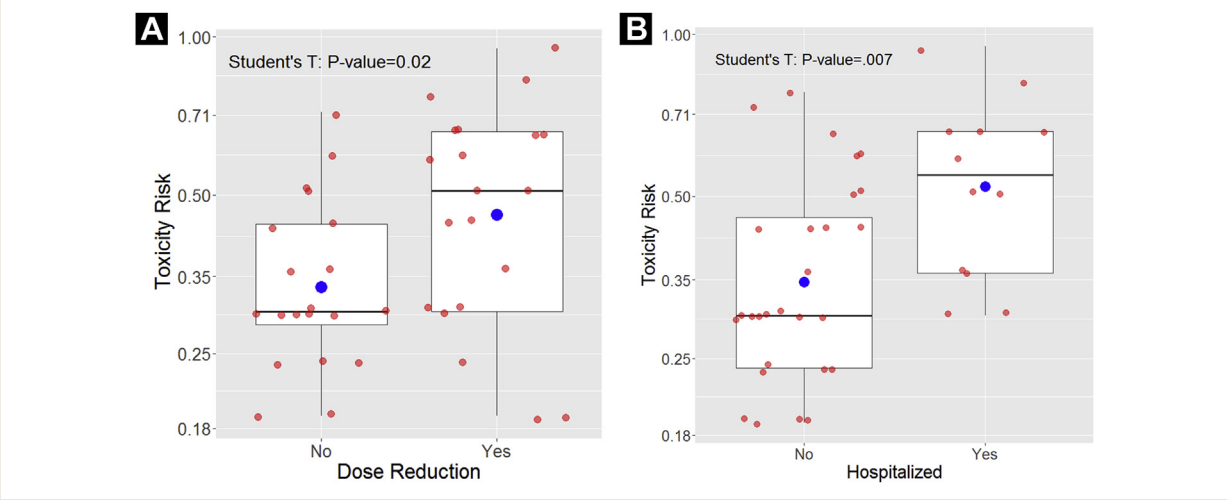
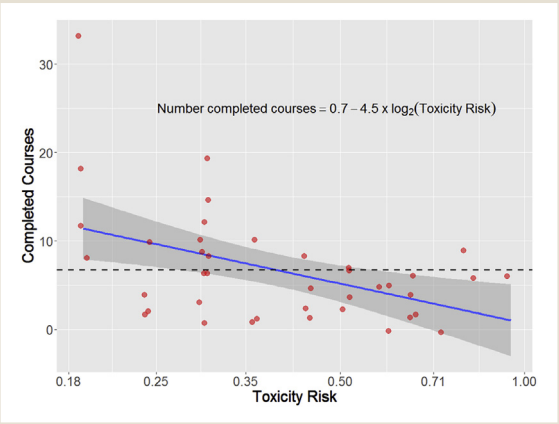


Figure 4 Association Between Toxicity Risk Score and Number of Courses Completed



chemotherapy toxicity risk score could identify patients who were less likely to tolerate treatment. This, in turn, could help clinicians and their older patients weigh the risks and benefits of treatment, ultimately personalizing cancer care.

Clinical Practice Points

Few clinical trials exploring the use of chemotherapy in metastatic breast cancer have focused on older patients.

nab-Paclitaxel may be an attractive option in older adults with metastatic breast cancer because it requires no premedication and has lower rate of hypersensitivity reactions.

In this phase II trial, we evaluated the tolerability and efficacy of *nab*-paclitaxel among women aged 65 years and older with metastatic breast cancer.

All patients underwent a cancer-specific GA, and a previously validated chemotherapy toxicity risk score was calculated for each patient. We explored the use of this risk score to predict chemotherapy-related toxicity, as well as the need for dose reductions, delays, and hospitalizations.

Forty older adults were included in the study. Fifty-eight percent had grade 3 or higher toxicities, and 30% were hospitalized owing to toxicity; 35% had an objective response to treatment. The median PFS was 6.5 months, and the median OS was 21.2 months. Patients with intermediate/high toxicity risk scores had higher risk of grade 3 toxicity than those with low risk scores. A higher mean risk score was associated with higher likelihood of dose reductions and hospitalizations.

A GA-based chemotherapy toxicity risk score could identify older patients who are less likely to tolerate treatment. This could help clinicians and their older patients weigh the risks and benefits of treatment, leading to improvements in personalized cancer care.

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Disclosure

A. Noonan declares consulting/advisory role for Helsinn Healthcare. G. Somlo declares consulting/advisory roles for Celgene, AstraZeneca, Abbvie, Pfizer, Takeda, and Puma Biotechnology; speakers' bureau for Takeda; research funding from Celgene, Roche, and Agendia. D. Li declares consulting/advisory roles for Lexicon, Novartis, and Ipsen; speakers' bureau for Lexicon. Y. Yuan declares consulting/advisory roles for Novartis and Pfizer; research funding from Eisai, Pfizer, and Merck. A. Hurria declares consulting/advisory roles for GTx, Boehringer Ingelheim, On Q Health, Sanofi, OptumHealth, Pierian Biosciences, and MJH Healthcare Holdings LLC; research funding from GSK, Celgene, and Novartis. J. Mortimer declares honoraria from Novartis; consulting/advisory roles from Puma Biotechnology, Pfizer, and Novartis. The remaining authors have stated that they have no conflicts of interest.

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JAMA Oncology | Original Investigation

Communication With Older Patients With Cancer Using Geriatric Assessment

A Cluster-Randomized Clinical Trial From the National Cancer Institute Community Oncology Research Program

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IMPORTANCE Older patients with cancer and their caregivers worry about the effects of cancer treatment on aging-related domains (eg, function and cognition). Quality conversations with oncologists about aging-related concerns could improve patient-centered outcomes. A geriatric assessment (GA) can capture evidence-based aging-related conditions associated with poor clinical outcomes (eg, toxic effects) for older patients with cancer.

OBJECTIVE To determine whether providing a GA summary and GA-guided recommendations to oncologists can improve communication about aging-related concerns.

DESIGN, SETTING, AND PARTICIPANTS This cluster-randomized clinical trial enrolled 541 participants from 31 community oncology practices within the University of Rochester National Cancer Institute Community Oncology Research Program from October 29, 2014, to April 28, 2017. Patients were aged 70 years or older with an advanced solid malignant tumor or lymphoma who had at least 1 impaired GA domain; patients chose 1 caregiver to participate. The primary outcome was assessed on an intent-to-treat basis.

INTERVENTIONS Oncology practices were randomized to receive either a tailored GA summary with recommendations for each enrolled patient (intervention) or alerts only for patients meeting criteria for depression or cognitive impairment (usual care).

MAIN OUTCOMES AND MEASURES The predetermined primary outcome was patient satisfaction with communication about aging-related concerns (modified Health Care Climate Questionnaire [score range, 0-28; higher scores indicate greater satisfaction]), measured after the first oncology visit after the GA. Secondary outcomes included the number of aging-related concerns discussed during the visit (from content analysis of audiorecordings), quality of life (measured with the Functional Assessment of Cancer Therapy scale for patients and the 12-Item Short Form Health Survey for caregivers), and caregiver satisfaction with communication about aging-related patient concerns.

RESULTS A total of 541 eligible patients (264 women, 276 men, and 1 patient did not provide data; mean [SD] age, 76.6 [5.2] years) and 414 caregivers (310 women, 101 men, and 3 caregivers did not provide data; mean age, 66.5 [12.5] years) were enrolled. Patients in the intervention group were more satisfied after the visit with communication about aging-related concerns (difference in mean score, 1.09 points; 95% CI, 0.05-2.13 points; $P = .04$); satisfaction with communication about aging-related concerns remained higher in the intervention group over 6 months (difference in mean score, 1.10; 95% CI, 0.04-2.16; $P = .04$). There were more aging-related conversations in the intervention group's visits (difference, 3.59; 95% CI, 2.22-4.95; $P < .001$). Caregivers in the intervention group were more satisfied with communication after the visit (difference, 1.05; 95% CI, 0.12-1.98; $P = .03$). Quality of life outcomes did not differ between groups.

CONCLUSIONS AND RELEVANCE Including GA in oncology clinical visits for older adults with advanced cancer improves patient-centered and caregiver-centered communication about aging-related concerns.

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Invited Commentary
page 204

Supplemental content

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Patient-centered communication promotes high-quality conversations prioritizing patient and caregiver concerns so that decisions are aligned with their preferences and values. Effective communication is characterized by (1) informed and participatory patients and caregivers; (2) informed, receptive, and patient-centered clinicians; and (3) a health care system providing well-organized and responsive services that are tailored to patients' and caregivers' needs.[1,2] Although studies have demonstrated benefits for interventions that facilitate oncologist-patient communication,[3-5] these interventions were not tailored to address aging-related concerns of older adults receiving cancer treatment and their caregivers.

Older adults represent most patients with advanced cancer seen in community oncology practices.[6,7] Cancer treatment choices for older adults with aging-related conditions (ie, disability, comorbidity, and geriatric syndromes)[8,9] are based on extrapolations of evidence derived from clinical trials that enroll younger patients or fit older adults.[10] Many older adults have unidentified, uncommunicated, and therefore unaddressed aging-related conditions that are associated with morbidity and early mortality.[11] A communication intervention for oncologists who care primarily for older adults—yet lack aging-related expertise—could improve patient and caregiver satisfaction by bringing attention to often-overlooked aging-related conditions.[12] Despite controversy,[13] satisfaction with physician communication is considered a metric for quality of health care and even modest improvements in survey scores are linked to increased reimbursement.[14-18]

To address a "cancer care delivery system in crisis,"[19(p1)] the National Academy of Medicine (formally the Institute of Medicine),[20,21] the American Society of Clinical Oncology (ASCO),[22] the Cancer and Aging Research Group,[10,23,24] and the International Society of Geriatric Oncology,[25] have all called for improved care delivery that attends to aging-related conditions of older adults with cancer. A key component is geriatric assessment (GA), which uses validated patient-reported and objective measures to capture domains important to older adults such as function (ie, ability to remain independent) and cognition. As highlighted in a recent ASCO guideline,[11] older adults and caregivers value these GA domains,[26,27] and GA domains, when formally assessed, influence treatment decision-making.[11,12,28-30] However, aging-related concerns are rarely addressed in oncology care, especially outside specialized academic settings.[12,31,32]

To our knowledge, this study is the first randomized clinical trial evaluating whether GA can meaningfully influence oncology care processes for vulnerable older adults with advanced cancer. With outcome measure selection guided by input from older patients and caregivers,[23,33] we hypothesized that providing GA information to oncologists would improve patient satisfaction with communication about aging-related concerns by increasing the number and quality of conversations during oncology clinic visits.

Key Points

Question Does providing a summary of geriatric assessment results and geriatric assessment–guided recommendations to oncologists improve communication about aging-related concerns?

Findings In this nationwide cluster-randomized clinical trial of 31 community oncology practices that enrolled 541 older patients with advanced cancer, providing a geriatric assessment summary with recommendations to oncologists improved postvisit patient satisfaction and caregiver satisfaction and increased the number of conversations about aging-related concerns. These results were significantly different between the intervention and usual care groups.

Meaning Integrating geriatric assessment into community oncology care improves patient and caregiver satisfaction and communication about aging-related concerns.

Methods

Overview

In this cluster-randomized clinical trial, Improving Communication in Older Cancer Patients and Their Caregivers (COACH), community oncology practices were randomized to the intervention or usual care group (CONSORT diagram in **Figure 1** and trial protocol in Supplement 1).[34] We enrolled participants from October 29, 2014, to April 28, 2017. The University of Rochester and all participating sites obtained approval from their institutional review boards. Participants provided written informed consent.

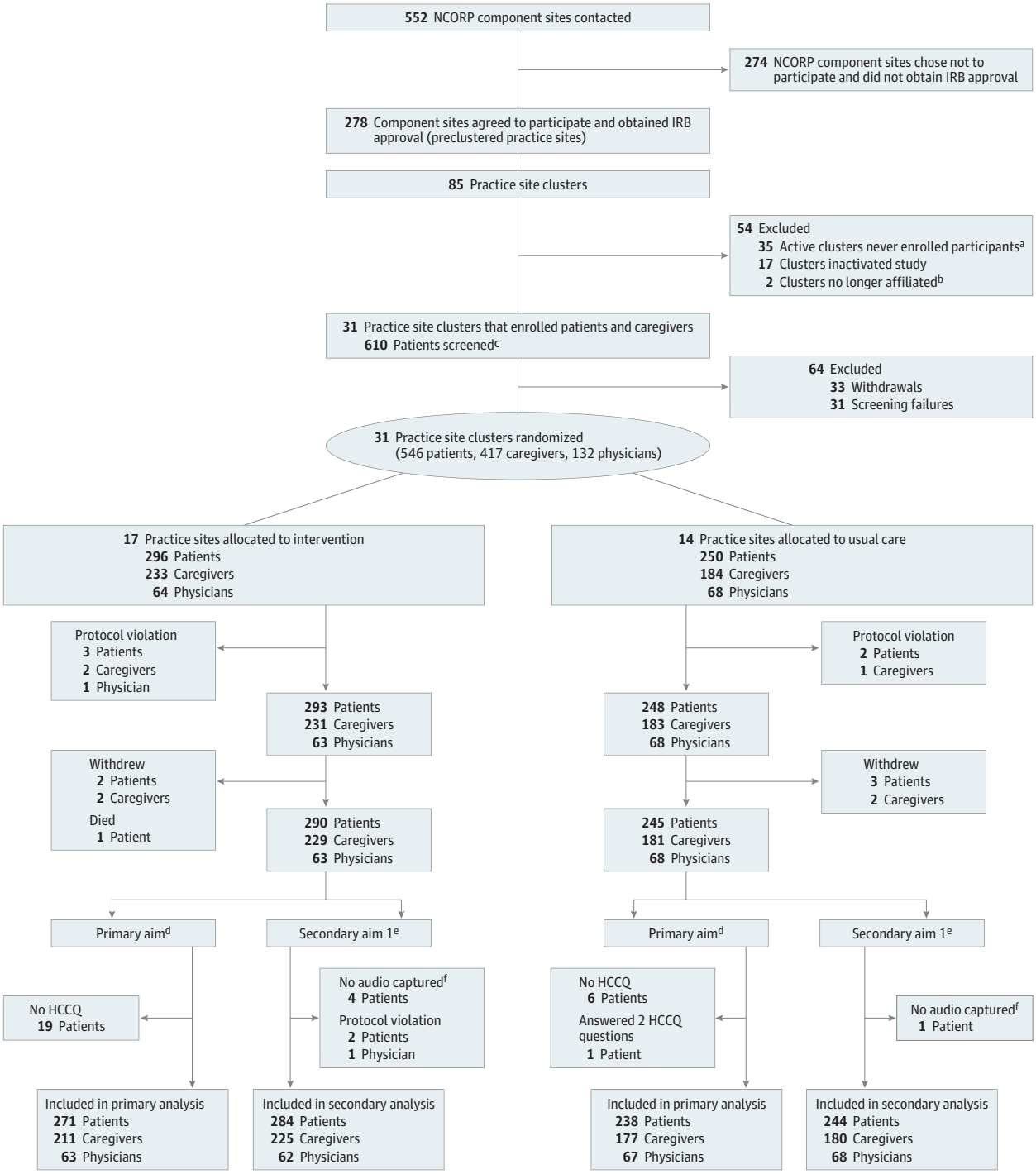
Settings and Participants

We recruited community oncology practices within the University of Rochester National Cancer Institute Community Oncology Research Program (NCORP) Research Base network. Oncologists enrolled as participants[12]; only patients of enrolled oncologists were eligible to participate. Other patient eligibility criteria included aged 70 years or older, at least 1 GA domain impairment,[11,25,35-37] an advanced solid tumor or lymphoma, cancer treatment with palliative intent, planned oncology visits for at least 3 months, ability to provide informed consent independently or via a health care proxy, and an understanding of English. Eligible patients chose 1 caregiver aged 21 years or older. Patients with no eligible caregivers could still enroll in the study.

Study Groups

All patients underwent a GA that evaluated 8 domains—functional status, physical performance, comorbidity, polypharmacy, cognition, nutrition, psychological health, and social support.[11,25,35-37] The GA was mostly patient reported.[37] Trained coordinators (J.G.) completed the objective performance and cognitive measures. At practices that were randomized to the intervention group, coordinators entered the GA scores into a locked web-based folder (http://www.mycarg.org) that created a tailored GA summary that was printed out for each patient. The summary included information on GA domain impairments and GA-guided recommendations based on literature review,[11] guidelines,[38] and expert consensus.[36] As an example, the summary would include information that a patient recently fell, that falls increase the risk of chemotherapy toxic effects, and a recommendation for physical therapy to prevent falls.[36] The summary and recommendations

Figure 1. CONSORT Flow Diagram for the COACH (Improving Communication in Older Cancer Patients and Their Caregivers) Trial of Practice Clusters, Oncologists, Patients, and Caregivers



Follow-up at 4 to 6 weeks included 472 patients, at 3 months included 410 patients, and at 6 months included 348 patients. Follow-up included 348 caregivers at 4 to 6 weeks, 306 caregivers at 3 months, and 261 caregivers at 6 months. HCCQ indicates Health Care Climate Questionnaire.

[a] Clusters that maintained institutional review board (IRB) approval but never enrolled any participants.

[b] Practices are no longer associated with their respective National Cancer Institute Community Oncology Research Program (NCORP) affiliate or with the University of Rochester NCORP Research Base.

[c] Signed consent and participated in screening process.

[d] Satisfaction with communication about aging-related concerns.

[e] Conversations about aging-related conditions during clinic visit.

[f] Irretrievable, site miscommunication, technical difficulty, or protocol violation.

were provided to oncologists once prior to an audiorecorded clinic visit. At study entry, oncologists received a brief training about GA and were told that they had autonomy for if and how they wished to use GA for their enrolled patients. For the usual care group, oncologists were alerted only if patients had abnormal scores on depression and cognitive tests.

Data Collection and Outcome Measures

In both groups, 1 oncology clinic visit within 4 weeks of GA was audiorecorded and transcribed. Within 7 to 14 days of this visit, trained personnel called the patient to assess satisfaction with communication. During the telephone call, the patients completed 2 versions of the Health Care Climate Questionnaire (HCCQ).[39,40] The first version measures satisfaction with patient-centered physician communication, such as whether the patient feels that the physician understands her or his perspective and encourages participation in decisions (score range, 0-20; higher scores indicate greater satisfaction). Similar to other research,[41] the second version of the HCCQ modified the language of the questions in the HCCQ to address satisfaction with communication regarding aging-related concerns (HCCQ-age; score range, 0-28); this modified version of the HCCQ was designed with input from advocates who were not enrolled in the trial and was used for the primary outcome (eAppendix in Supplement 2).

A secondary outcome included the number of aging-related concerns discussed at the visit. With experts and 4 coders, a content analysis framework[42] outlined how to identify aging-related conversations, assess their quality (whether a concern was acknowledged and further explored by the oncologist), and determine whether an acknowledged concern motivated recommendations for specific GA-guided interventions.[3,11,31,32,36,43] Team coding of the transcribed audiorecordings occurred until interrater reliability[42] was 70% or greater. Subsequently, for each transcript, coding was performed independently by 2 trained coders, with 20% of transcripts coded by all 4 coders. Final interrater reliability was 82% for number of concerns and 92% for both quality and interventions.

Other secondary outcomes evaluated patient and caregiver quality of life (QoL) as well as caregiver satisfaction with communication. Patients completed the Functional Assessment of Cancer Therapy scale[44] at enrollment and 4 to 6 weeks, 3 months, and 6 months later. Caregiver QoL was assessed using the 12-Item Short Form Survey[45] and burden was assessed using the Caregiver Reaction Assessment[46] at the same time points as patients. Caregivers completed HCCQ surveys that assessed their satisfaction with communication about their concerns related to the patient's aging-related conditions and overall care (score range for both surveys, 0-20).

Randomization and Blinding

Accrual records from University of Rochester NCORP studies were used to stratify practice clusters as large or small accruing sites to assure balance in randomization. Randomization was done at the practice cluster level and recruitment of all participants was based on the group to which their practice cluster was assigned. Other than the statisticians, all investigators were blinded to group; blinding was preserved among the telephone team, transcriptionists, and coders.

Sample Size

Sample size and power considerations were based on the primary aim of the HCCQ-age to address patient satisfaction with communication about aging-related concerns. This design had 80% power at the 0.05 significance level to detect a difference of 1.3 in HCCQ-age scores, with an intraclass correlation coefficient (ICC) of 0.14,[3,32] corresponding to an effect size of 0.62. Assuming a withdrawal rate of 5% (based on observational cohort data[47]), the targeted accrual was 528 patients. The design had 80% power at the 0.05 significance level to detect a difference of 0.46 in the number of conversations about aging-related concerns, with an ICC of 0.12, corresponding to an effect size of 0.59.[32] We originally aimed for participation by 16 NCORP practices. Because the recruitment was initially slower than anticipated, we allowed more practices to participate (as specified by the trial protocol in Supplement 1). The total patient sample size did not change.

Statistical Analysis

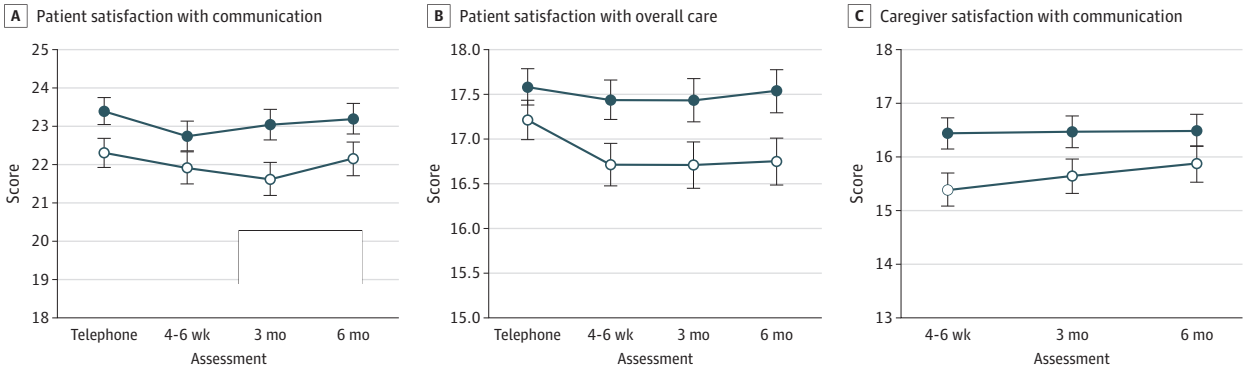
Descriptive statistics were used to evaluate demographics, GA results, and clinical information, and bivariate analyses were performed to compare between- group differences in characteristics of patients and caregivers. For the primary outcome, to follow the intent-to-treat principle and to assess the effect of missing values on the study results, we conducted additional analyses including all randomized eligible patients. Under missing at random assumptions, we evaluated the influence of missing data on the study results via multiple imputation.[48] The examination of the reasons for missing data did not reveal any reason to suspect a missing not at random mechanism. Nevertheless, we also applied sensitivity analysis using pattern mixture models.[49] Similar to prior research,[50,51] we conducted responder analyses evaluating the proportion of participants who reported satisfaction scores within a half SD of the HCCQ score from the perfect score; achieving a perfect satisfaction score is commonly advocated as a metric for high quality in practice.[52,53]

Because of the cluster-randomized study design, a linear mixed model method was applied.[54] The outcome was the response, and the group was the fixed effect. Practices were entered as a random effect independent of residual error. Estimation was performed using restricted maximum likelihood, and the null hypothesis of zero mean difference between groups was tested using an F test.[55] The results are presented as means (or mean difference) adjusted for the practice effect and evaluated as marginal means from the linear mixed model. Practice differences were assessed graphically using best linear unbiased predictors of the mean response for each.

To assess the effect of the intervention on the outcomes over time, we used a longitudinal linear mixed model. An unstructured correlation matrix was used for the repeated measures from the same participant. The model was adjusted for practice cluster using a random effect independent of the within-participant random effects, and it was fit via restricted maximum likelihood.

Every effort was made to facilitate participants' completion of questionnaires. However, baseline data from some participants were missing, and there was participant withdrawal

Figure 2. Patient and Caregiver Satisfaction



A, Patient satisfaction with communication about aging-related concerns. B, Patient satisfaction with overall care. C, Caregiver satisfaction with communication about the patient's age-related conditions. Scores were derived using modified versions of the Health Care Climate Questionnaire. The telephone assessment was 7 to 14 days after the audio-recorded clinic visit.

(Figure 1); anticipating that some patients would not be able to be reached by telephone, the protocol allowed for imputation of the 4- to 6-week HCCQ results to assess the primary aim. Analysis was performed with SAS, version 9.4 (SAS Institute Inc) and R, version 3.5.2 (R Foundation for Statistical Computing) software. All *P* values were from 2-sided tests, and the results were deemed statistically significant at $P < .05$.

Results

Participant Characteristics

From October 29, 2014, to April 28, 2017, 31 practice clusters (17 intervention and 14 usual care) enrolled participants, including 131 oncologists, 541 eligible patients, and 414 eligible caregivers (Figure 1). Patients had a mean (SD) age of 76.6 (5.2) years (range, 70-96 years), and 264 (48.8%) were women; most patients had gastrointestinal and lung cancers (278 [51.4%]) and were receiving chemotherapy (369 [68.2%]) (eTable 1 in Supplement 2). There were no essential differences in demographics or clinical characteristics by group. Most patients had 2 or more GA domain impairments (mean [SD], 4.5 [1.5]); the prevalence of GA domain impairments ranged from 93.7% (n = 507) for physical performance to 25.1% (n = 136) for psychological status; 180 patients (33.3%) had possible cognitive impairment. A total of 487 of 541 patients (90.0%) had 3 or more GA domain impairments. More patients in the usual care group had impaired physical performance (239 of 248 [96.4%] vs 268 of 293 [91.5%]; $P = .03$) and social support (82 of 248 [33.1%] vs 74 of 293 [25.3%]; $P = .05$) (eFigure in Supplement 2). Caregivers (n = 414; mean [SD] age, 66.5 [12.5] years; range, 26-92 years) were most likely to be the patient's spouse or partner (276 [66.7%]; eTable 2 in Supplement 2) and 310 [74.9%] were women. Baseline data for oncologists,[12] patients,[37,56,57] and caregivers[37,56,57] have been published.

Patient Satisfaction With Communication

For 509 evaluable patients, the mean (SE) satisfaction score for communication about aging-related concerns was 22.8 (0.27) (range, 5-28 for HCCQ-age) after the clinic visit. The score in the intervention group was 1.09 points higher than in the usual care group (95% CI, 0.05-2.13; $P = .04$; ICC = 0.02). After the clinic visit, the mean (SE) satisfaction score for communication about overall care was 17.4 (0.16) (range, 5-20 for HCCQ). The proportion of patients within a half SD from a perfect score was higher in the intervention group (109 of 271 [40.2%] vs 71 of 238 [29.8%]). Over 6 months, patients in the intervention group were more satisfied with communication about aging-related concerns (difference in mean HCCQ-age score, 1.10; 95% CI, 0.04-2.16; $P = .04$) (**Figure 2**A) and reported greater satisfaction with overall care (difference in mean HCCQ score, 0.70; 95% CI, 0.06-1.25; $P = .03$) (Figure 2B).

Number and Quality of Conversations About Aging-Related Concerns

For 528 evaluable patients, the adjusted mean (SE) number of conversations about aging-related concerns during the oncology clinic visit was 6.34 (0.48) (range, 0-18). There was an adjusted mean of 8.02 conversations in the intervention group compared with 4.43 in usual care (difference, 3.59; 95% CI, 2.22-4.95; $P < .001$; ICC = 0.14; **Figure 3**). The intervention group had an adjusted mean of 4.60 high-quality conversations, compared with 2.59 in the usual care group (difference, 2.01 [adjusted by practice site]; 95% CI, 1.20-2.77; $P < .001$; ICC = 0.06). There was an adjusted mean of 3.20 conversations about recommendations in the intervention group compared with 1.14 in the usual care group (difference, 2.06; 95% CI, 0.99-3.12; $P < .001$; ICC = 0.30). eTable 3 in Supplement 2 is a joint display[58] illustrating exemplar quotes with mean conversation numbers by domain.

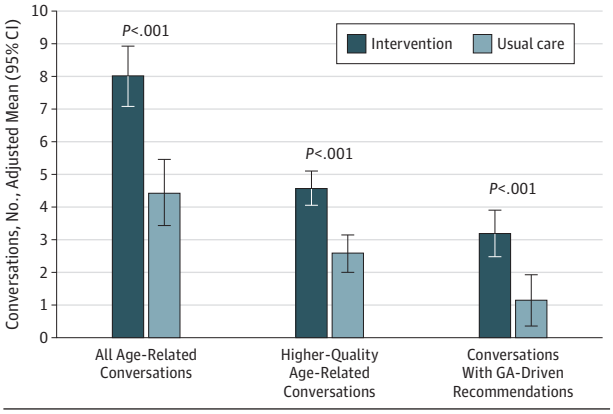
Patients' and Caregivers' Health-Related Quality of Life

Analyses did not detect any statistically significant differences between groups in Functional Assessment of Cancer Therapy scale score for patients over 6 months (range, 23-108; difference [SE], −0.23 [1.03]; $P = .82$). In addition, there were no differences for caregiver 12-Item Short Form Survey total scores or Caregiver Reaction Assessment subscales.

Caregiver Satisfaction With Communication

At 4 to 6 weeks after the clinic visit, caregivers in the intervention group were more satisfied with their communication regarding their concerns about the patients' aging-related conditions (range, 5-20; difference, 1.05; 95% CI, 0.12-1.98; $P = .03$). The proportion of caregivers within a half SD of a perfect score was higher in the intervention group (74 of 189 [39.2%] vs 42 of 158 [26.6%]). Caregivers were more satisfied with their own communication with oncologists with regard to overall care (range, 2-20; difference, 1.34; 95% CI, 0.50-2.18; $P = .004$). The differences in satisfaction scores were not significant when analyzed over 6 months (Figure 2C).

Figure 3. Conversations About Aging-Related Conditions



The patient's visit with the oncologist within 4 weeks of completing the geriatric assessment (GA) was audiorecorded, transcribed, and coded. We used an open coding approach of themes and subthemes to quantify the number of age-related conversations, the number of aging-related discussions with high-quality communication, and the number of conversations of GA-driven recommendations communicated to patients by oncologists.

Discussion

The COACH cluster-randomized clinical trial is the first large multisite intervention study to demonstrate that providing a GA summary with GA-guided recommendations to community oncologists facilitates communication about aging-related concerns and improves patient and caregiver satisfaction with communication and care. COACH enrolled vulnerable older patients with cancer who had significant aging-related conditions—90% had 3 or more GA domain impairments. These patients represent less-fit individuals for whom there is limited evidence for the risks and benefits of cancer treatment,[59] yet these patients are commonly seen in real-world community practices. Although patients had various cancer types, all were incurable and were treated with palliative intent.

Evidence increasingly supports the use of GA for evaluation and management of older patients with cancer to guide shared decision-making between older patients, caregivers, and oncologists.[11,25] As highlighted in the ASCO geriatric oncology guidelines[11] and supported by systematic reviews,[29,60] GA impairments are associated with chemotherapy toxic effects, lower treatment completion, functional decline, early mortality, and higher health care use. Like others, we found that older patients with a high prevalence of GA domain impairments still receive treatment for advanced cancer, including chemotherapy. Of particular concern is the one-third of patients who had positive screening results for possible cognitive impairment, given the limited evidence for the safety and efficacy of chemotherapy in this group.[61] The higher prevalence of GA domain impairments compared with other trials reflects our expanded eligibility criteria and our use of a formal GA to evaluate often overlooked aging-related conditions.

Despite patient and caregiver concerns and preferences for maintaining function and cognition,[26,27] oncologists often do not discuss implications of aging-related conditions or inform older patients and caregivers of heightened risk of adverse events from treatment.[32] We found that, when GA information was provided, community oncologists used it in communication during the clinic visit, similar to other nongeriatric studies that have systematically provided symptom and QoL information to oncologists.[62,63] Our results align with this research showing that coordinated care for younger patients that captures patient-reported outcomes improves quality of care and outcomes; for older patients with cancer, personalized care requires attention to aging-related conditions.

We recruited older patients who had several different cancers and treatments, which may have limited our ability to detect QoL effects. In addition, the intervention provided a GA summary during 1 clinic visit only to oncologists; studies that have reported survival and QoL benefits from structured interventions have incorporated evaluation and management of patient-reported outcomes over time[64] or have used geriatrics-trained professionals.[29,64] A randomized study of GA-directed therapy for older patients with advanced lung cancer demonstrated reduced toxic effects of treatment and less treatment discontinuation in the GA group owing to improved treatment allocation.[65] Several ongoing clinical trials will evaluate if GA can help improve clinical outcomes (QoL, toxic effects, and survival) of patients through improved decision-making and GA-guided interventions.[11]

A previous study using baseline COACH data reported that an increasing number of patient GA domain impairments is associated with poor caregiver emotional health and QoL.[37] Similar to early palliative care models that used specialized nurse coaches to assess and provide management for patients and caregivers, GA-based interventions could be adapted for both patients and caregivers.[66]

Strengths and Limitations

Strengths of this study include recruitment of a large sample of vulnerable older patients and their caregivers who have rarely been included in cancer trials. This study also demonstrates the ability to conduct multisite trials incorporating GA in the community oncology setting. We attribute our successful completion of the trial in large part to our patient and caregiver research advocate partners from Scoreboard (Stakeholders for Care in Oncology and Research for our Elders) who provided ongoing input and solutions for barriers.[23,33]

Limitations include risk of selection bias, as we enrolled a specific population of older patients; however, these are patients who are commonly seen in community oncology clinics and are underrepresented in research. Although cluster randomization is a strength, since we were testing a model of care as an intervention, there is a risk of selection bias inherent in cluster randomization.[67] Oncologists in both groups were not blinded, and thus may have modified their discussions of aging; however, the strength of the findings shows that modifying oncologist behavior to increase communication about aging-related concerns is possible.

Conclusions

To our knowledge, the COACH cluster-randomized clinical trial is the first trial to demonstrate that provision of a formal GA to community oncologists, per ASCO guidelines,[11] can improve satisfaction and communication for vulnerable older patients with advanced cancer and their caregivers. COACH demonstrated that a practical and convenient GA summary with recommendations for aging-sensitive interventions improves patient-centered outcomes and thus should be considered as the standard of care for older patients with cancer.

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Invited Commentary

Expanding the Scope of Geriatric Assessment for the Management of Cancer in Older Adults

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Cancer is a disease of older adults, with approximately 50% of cancer cases and 70% of cancer-related deaths occurring in individuals older than 65 years.[1] Older adults are also the fastest-growing portion of the general population worldwide,[2] which suggests that the incidence of cancer in this age group will continue to increase. Managing cancer in older adults poses a significant challenge to oncologists and health care systems because they represent a very heterogeneous population with organ-specific physiological changes and a diverse burden of functional impairments, comorbidities, polypharmacy, geriatric syndromes, and cognitive, nutritional, and psychological issues. All these factors may increase the risk of adverse events from anticancer treatments and complicate decision-making. In addition, the basis of evidence to guide the management of cancer in this group is limited, as therapeutic trials tend to enroll a very select population of patients.

Related article page 196

Chronological age alone does not reflect the unique complexity of older adults, nor does it differentiate apparently fit individuals who are actually at risk of unexpected toxic effects secondary to anticancer therapies from supposedly "frail" individuals who in fact do not require any modified treatment plan. Geriatric assessment (GA) represents the most appropriate solution to this conundrum. Its benefits for older patients with cancer have been widely demonstrated and include the prediction of complications and functional decline while undergoing anticancer treatment, the estimation of survival, the facilitation of treatment decision, the detection of problems usually neglected by routine history and physical examination at baseline and during follow-up care, and the improvement of mental health, well-being, and pain relief. The inclusion of GA in oncology practice is now endorsed by increasing consensus worldwide.[3]

In this issue of *JAMA Oncology*, Mohile et al[4] provide further rationale in support of the implementation of GA in routine cancer care. In a multicenter cluster randomized clinical trial, the authors demonstrate that GA can enhance the satisfaction of patients and caregivers after consultation in a community setting and yield the opportunity for communication to focus on issues related to aging. This study—which mobilized 31 community oncology practices to

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Geriatric assessment among older adults receiving intensive therapy for acute myeloid leukemia: report of CALGB 361006 (Alliance)

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Abstract

Objective: To demonstrate feasibility of performing geriatric assessment (GA) in the National Clinical Trials Network (NCTN) and to explore the utility of GA to characterize treatment tolerance.

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H.D.K. and E.R. designed the research, performed research, interpreted analyses, and wrote and edited the manuscript. B.S. and K.B. designed research and edited the manuscript. B.M.E, J.LR, analyzed data, contributed to manuscript preparation and edited the manuscript. D.S., L.S., S.G. W.Z. analyzed data and edited the manuscript. G.M., B.L, M.B., W.S., R.S., R.L., G.U. contributed to study design, performed research and edited the manuscript. HJC contributed to research design, data interpretation and edited the manuscript.

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Conflict of interest statement:

The authors have no conflicts of interest to report.

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Materials and Methods: We conducted a multisite companion study (CALGB 361006) to CALGB 11001, a phase 2 trial of adults ≥60 years old with newly diagnosed FLT3- mutated AML, testing the efficacy of adding sorafenib to intensive chemotherapy. On 361006, a GA was administered prior to induction and prior to post-remission therapy. The GA is divided into items requiring administration by a health care professional (HCP) and patient self-administered questionnaires. Feasibility outcomes were recruitment rate, time to GA completion, difficulty with GA administration, percent of patients requiring assistance, and satisfaction. Change in GA measures pre- and post-induction were compared using Wilcoxon signed rank test and McNemar's tests.

Results: The recruitment rate was 80% (N=43, median age 68 years). Median completion time of the GA was 30 minutes; (10 and 21 minutes for HCP and patients, respectively). HCP reported no difficulty completing assessments (100%). Most patients completed questionnaires without assistance (77%), and were satisfied with the length (89%). Self-reported physical function, mental health, social activity and nutritional parameters worsened after induction.

Conclusion: GA is feasible to administer in the setting of intensive induction for older adults with AML in the NCTN and provides evidence of the impact of induction therapy on physical and emotional health.

Keywords

acute myeloid leukemia; leukemia; older; age; geriatric assessment; feasibility; hematology; hematologic malignancy

Introduction:

Acute myeloid leukemia (AML) is a disease most commonly diagnosed in older adults. Survival for patients with AML is age dependent, with significantly lower survival rates reported for older adults.[1,2] While selected older adults may benefit from aggressive therapies, older adults, as a group, are at risk for increased toxicity from treatment. [1,3,4] Assessment tools are needed to better characterize fitness in the context of therapy and to capture how older adults feel and function prior to and after therapy. This information could assist clinicians in making treatment decisions, inform future trial design, and identify potentially modifiable risk factors for development of interventions to improve treatment outcomes and the quality of survivorship.

Geriatric assessment (GA) is a strategy that can characterize the heterogeneity of aging and capture important functional outcomes for older adults. Based on single institution data, pretreatment GA for older adults with newly diagnosed AML appears feasible.[5] In this setting GA detects significant, potentially unrecognized, impairments in the majority of patients scheduled to receive intensive therapy despite good performance status. [5] Importantly, GA measures such as objectively measured impaired physical function and cognitive performance are independently associated with worse survival among intensively treated patients.[6] Similarly, a fitness score derived from clinical and GA parameters has also been associated with survival among older adults with AML or myelodysplastic syndrome receiving non-intensive therapies.[7] Retrospective studies evaluating specific patient

characteristics such as comorbidity, polypharmacy, and symptoms further support the importance of comprehensive and standardized risk assessment strategies for older adults.[7-11] However, the feasibility and utility of GA has not been demonstrated in multisite AML National Cancer Institute (NCI) National Clinical Trials Network (NCTN) studies.

A brief, comprehensive, standardized GA to characterize a patient's "functional age" was developed in the Alliance for Clinical Trials in Oncology (Alliance) Cancer in the Older Adult Committee and was previously piloted in a multisite trial among older adults scheduled to receive chemotherapy predominantly for solid tumors.[12,13] The assessment evaluates functional status, comorbid medical conditions, cognition, nutritional and psychological status, social support and social activities and was feasible to administer to patients enrolling on non-AML NCTN trials. A toxicity risk score derived from this GA predicts chemotherapy toxicity.[14,15] These published data, however, do not include patients with newly diagnosed AML. AML diagnosis and treatment represents a unique, often high-acuity setting, requiring rapid diagnosis and initiation of treatment commonly in the inpatient setting. It is uncertain whether data from non-AML studies can be extrapolated to the care paradigm for AML. To address this issue, the primary objective of this study was to evaluate the feasibility of performing GA in an AML NCTN treatment trial. Secondary objectives were to investigate the impact of induction chemotherapy on physical, cognitive, psychosocial factors and explore the association of baseline GA measures with overall survival.

Methods:

Cancer and Leukemia Group B (CALGB) 361006 was a prospective multisite embedded companion study offered to patients enrolled on CALGB 11001 at the 15 participating CALGB institutions. CALGB 11001 was a phase II study of adults 60 years of age or older with newly diagnosed FMS-like tyrosine kinase-3 (*FLT3*) mutated AML testing the efficacy of adding sorafenib to intensive chemotherapy with daunorubicin and cytarabine open between 2011 and 2014.[16] Any site participating in CALGB 11001 could enroll on 361006. This study, with the 361006 companion, was approved by the NCI Central Institutional Review Board and by the institutional review board (IRB) at each participating institution. CALGB is now part of the Alliance for Clinical Trials in Oncology.

Eligibility criteria

Patients were eligible to enroll on the GA companion study (CALGB 361006) if they met eligibility criteria for and enrolled on CALGB 11001. Briefly, eligibility criteria for the treatment and companion study included: a new histologic diagnosis of AML excluding acute promyelocytic leukemia and core binding factor leukemia; documented FLT3 mutation determined by central laboratory; 60 years of age or older; and no prior chemotherapy for AML. The minimum acceptable performance status or laboratory parameters were not specified.

Procedures

Before patients were enrolled in CALGB 361006, the study principal investigator (HDK) trained research staff at each participating site (via telephone). Training calls (approximately 15-30 minutes) in length reviewed written standardized administration and scoring instructions for each GA measure and provided an opportunity for staff to ask clarifying questions. Then, patients who were eligible to enroll on CALGB 11001 were offered the opportunity to enroll on CALGB 361006. All patients who chose to participate in the GA companion study (361006) completed an IRB-approved, protocol-specific informed consent at the time of consent to the treatment trial (CALGB 11001). The GA and a quality-of-life questionnaire were completed at baseline (prior to initiation of induction chemotherapy) and again after induction at the time of evaluation for consolidation therapy either in the inpatient or outpatient setting. Patient registration, data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. The study chair contacted site staff to obtain reasons for missing data when one was not provided.

Measures

The GA tool includes validated measures assessing the domains of physical function, comorbid medical conditions, psychological state, social activities and support, nutritional status, cognitive function and medications.[12,13] It was developed for use in the NCTN setting with a full description of measures previously reported. Modifications to the GA tool for this study include the addition of the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI)[17] and the substitution of the Mental Health Inventory-17 (MHI-17) to assess psychological health.[18] The HCT-CI was added because it is well validated in leukemia and provides more detailed information on comorbidity burden than the patient-reported comorbidity assessment included in the GA.[19-21] The MHI-17 was chosen as a substitute assessment for psychological health by the Alliance Cancer in the Older Adult Subcommittee due to the proprietary nature of the previously included measure.

The GA tool includes a healthcare provider (nurse or certified research associate) administered assessment and a self-administered patient questionnaire. The healthcare provider-administered questionnaire included the following 5 brief assessments: 1) HCT-CI (a validated comorbidity index associated with remission status and survival among older adults with AML)[17,19,21]; 2) Karnofsky performance status; 3) Timed up and Go (a performance based measure of physical function; time assessed in seconds for those who could complete the test or recorded as unable to perform)[22]; 4) Blessed Orientation Memory Concentration test (score ≥11 indicating impairment)[23]; 5) recording of height and weight (current and 6 months prior) to evaluate nutritional status including calculation of body mass index. Prior weight was collected by self-report if not recorded in the medical record. Intentionality of weight loss was not assessed.

The self-administered patient questionnaire included several validated surveys and demographic questions. The questionnaire included self-reported measures of physical function and activities (inclusive of activities of daily living, instrumental activities of daily

living and mobility items), a patient-rated Karnofsky performance status, self-reported falls in the past 6 months, self-reported comorbid conditions and a rating of the degree to which each causes interference in activities, number and type of medications, assessment of psychological state (symptoms of anxiety and depression), social activity, and social support. A member of the health care team could assist those patients who needed help.

Health-related quality-of-life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). [24,25] Domains assessed included general physical symptoms, fatigue and malaise, and physical, social and emotional functioning. Time points for assessment were the same as for the GA questionnaires.

Outcomes

The primary outcome was feasibility evaluated by recruitment of participants, implementation (time to completion, difficulty with administration, percent of participants requiring assistance), and patient satisfaction with the assessment. Time to completion of the battery of tests was estimated in minutes by the health care professional for both portions of the evaluation. The research team completed survey questions about difficulty with administration. Staff was asked whether any items were difficult to administer or difficult to complete by the staff or participant. To determine patient satisfaction with the assessment, the patient questionnaire surveyed participants regarding difficulty understanding questions, length of the assessment, whether items were upsetting and whether important questions were left out. Similar to prior feasibility work in the NCTN setting, feasibility thresholds were recruitment rate of 70%, no difficulty in implementation reported by ≥70% of participants and ≥ 80% of research staff and ≥80% of participants reporting satisfaction.[12] A time to completion indicating feasibility of the entire assessment was ≤ 40 minutes.

Secondary outcomes included: 1) evaluation of the change in GA measures from baseline to after induction assessment; 2) exploration of relationships between specific baseline GA measures and overall survival to inform larger trials; and 3) description of health care utilization by capturing hospitalizations, oncology clinic visits and nursing home use during the study from the medical record. OS was estimated from the time of signing the consent form.

Statistical analyses

Descriptive statistics were used to summarize feasibility outcomes and GA measures. Continuous variables were described by mean (standard deviation) and median (range) and categorical variables by frequency and percentage. Changes from baseline to post-induction therapy were calculated using the Wilcoxon signed rank test for continuous variables and McNemar's test for categorical variables. Survival probabilities were estimated using the Kaplan-Meier estimator.[26] Associations between baseline GA measures and overall survival were explored by comparing survival probabilities between groups (dichotomized by the median score due to small sample size) using the log-rank test. All analyses were performed using SAS Version 9.3 (SAS Institute, Cary NC, USA) and had a two-sided alpha level of

0.05. Data lock for trial data was on May 11, 2016. Due to the exploratory nature of this analysis, there was no adjustment for multiple comparisons.

Results:

Among the 54 patients who enrolled on clinical trial CALGB 11001, 43 (80%) enrolled on the GA companion study (CALGB 361006) from 14 different institutions (Figure 1). Of these, 40 completed at least one baseline assessment (93%). Twenty-eight patients (70%) performed a follow-up assessment after induction therapy. Of those who did not complete follow-up assessment, 3 were deceased, 3 came off study treatment (1 for resistant disease) and 6 assessments were missed (reasons not documented).

Baseline characteristics are presented in Table 1. Nearly 40% of participants were aged 70 years and above. Most were non-Hispanic, white males. The majority (75%) received one cycle of induction therapy. The remission rate was 78% and 64% received post-remission therapy. The early death rate was 10% and median overall survival was 14.9 months (95% C.I. 12.6-23.3 months). Tumor and treatment characteristics of the GA cohort were similar to the overall study cohort.[16]

The median time recorded for completion of the GA battery inclusive of both the health care professional and patient questionnaires was 30 minutes (Interquartile range 23-40 minutes). The median times recorded for completion of the health care professional questionnaire was 10 minutes (range 2-30 minutes) and for the patient questionnaire was 23 minutes (range 3-90 minutes). Among research staff, 100% reported no difficulty administering the healthcare professional component. The majority of patients reported no difficulty understanding questions (89%) and completed the assessment without assistance (77%). Patient satisfaction was high; 89% were satisfied with the length and no patients found the questionnaire upsetting.

Baseline values for each GA measure and the quality-of-life questionnaire (EORTC CLC-Q30)are presented in Table 2. Most participants reported independence in instrumental activities of daily living, had good performance status, had no history of falls, screened negative for cognitive impairment, were taking on average 4.5 medications and had modest comorbidity burden. Mean scores were low for psychological state, social activity and social support scales, and global quality-of-life measures (indicating prevalent psychological symptoms, less social activity and support, and poor quality of life). Mean scores on the Timed Up and Go test indicated impaired mobility (≥11 seconds) although the majority (90%) were able to perform the test.

For patients who completed post-induction assessment, change in GA measures and global quality-of-life is presented in Table 3. Receipt of induction therapy had a variable impact on GA measures for the 28 patients who survived induction therapy and returned for evaluation of post-remission therapy. Self-reported physical function (assessed by instrumental activities of daily living), psychological state, social activity, body mass index and unintentional weight loss significantly worsened. By contrast the global quality-of-life (EORTC CLC-Q30) score improved. Scores on the emotional, social, and several symptom-

related subscales (pain, dyspnea, appetite) of the EORTC CLC-Q30 significantly improved after induction ($p<0.05$ for all) and none showed significant worsening (data not shown).

Exploratory analyses investigating the relationship between baseline GA measures and overall survival did not show any statistically significant associations. Univariate results are shown in Table 4; they can be useful to estimate effect size for larger studies. For example, the hazard of mortality was higher for those with self-reported physical limitations (lower scores on MOS physical health subscale and Instrumental Activities of Daily Living) and for those reporting a fall. Similarly, there was no association between baseline global quality-of-life measured by EORTC CLC-Q30 and survival. However, the nausea/vomiting subscale of the EORTC CLC-Q30 was associated with worse survival; those with symptoms at baseline had an OS of 0.8 years compared to those without at 1.6 years ($p=0.007$).

Health care utilization for participants who survived induction was high, with data available from 25 of 28 individuals. The median (range) number of days hospitalized for chemotherapy during the time between diagnosis and start of consolidation was 30 (7 – 61). In addition, roughly 27% were re-hospitalized for reasons other than chemotherapy during this period with a median of 25 (3 – 47) days. The median number of oncology clinic visits was 2.0 (0 – 4); 1 participant required care in a nursing facility for rehabilitation or long-term care.

Discussion:

This is the first multisite NCTN study to demonstrate that GA is feasible and useful for older adults treated intensively for AML, despite the acuity and complexity of the disease setting. The wide range of scores for individual GA measures support the role of using this tool to better categorize the heterogeneity of aging and to identify potentially unrecognized vulnerabilities that can impact treatment outcomes and survivorship. GA measures post induction highlight the impact of treatment on functional domains and quality of life and provide potential targets for interventions to improve them. These findings support further investigation of GA in the context of clinical trials for AML to inform risk prediction and tailored supportive care.[27]

This study is consistent with others demonstrating the feasibility of incorporating GA strategies into multisite trials in the non-AML setting.[12,28] Our results support the generalizability of incorporating GA into the evaluation of older adults receiving intensive therapy for AML, previously shown in a single institution trial.[5] Assessments were well received by both patients and research staff, and the time required was considered acceptable, with no reported concerns about participant or staff burden. Compared to implementation of the same GA in a predominantly solid tumor population, the median time required was slightly longer (30 vs. 22 minutes) with a small increase in the proportion of AML patients requiring some assistance (77% vs. 87%) and with similar high degrees of patient satisfaction.[12]

This pilot also identifies opportunities to enhance efficiency, further minimize potential burden, and maximize value. First, training on measure administration using online

educational modules that are now available for NCTN trials could enhance efficiency for sites when opening trials that include GA. Second, the follow-up GA can be further streamlined by tailoring assessments to those measures demonstrating change over time. Use of tablets for direct data capture can further minimize missing data and staff time.[29,30] Attrition is a particular challenge in a dynamic patient population with high morbidity. While some attrition is unavoidable, collecting the GA/patient-reported outcome data as an integrated part of the treatment trial, rather than as a companion study requiring separate consent, can maximize participation and further minimize opportunities for missed assessments.

Similar to studies using GA in other settings, we demonstrate that older adults deemed fit for intensive chemotherapy have significant heterogeneity in physical function, cognition, comorbidity, emotional health, rates of polypharmacy, nutritional status, social activities and social support.[31] This observation provides proof-of-principle that incorporating GA into AML therapy can help characterize the heterogeneity of aging in this context. Compared to results from an observational study of older adults with predominantly solid tumor malignancy using the same GA, patients in the current study had slightly higher levels of self-reported physical function at baseline with higher levels of psychological distress.[15] However, similar to results among solid tumor patients, more than half had impaired objectively measured physical function (Timed Up and Go score >10 seconds) reinforcing the importance of capturing objective measures to characterize vulnerabilities.[6,15,32]

Our study adds to the literature by using GA and a global health-related quality-of-life measure concurrently as outcomes after intensive induction therapy to help characterize treatment tolerance. The impact of treatment on quality of life and independence is critical to inform decision-making and targeted supportive care for older AML patients. Yet only limited data have been collected in clinical trials for outcomes such as physical function, cognition, and psychological health. In a review of over 1000 clinical trials in hematologic malignancies, less than 10% collected endpoints related to quality of life, physical function or health care utilization.[33]

In this study, participants evaluated for post-remission therapy reported increased physical limitations, worse mental health, decreased social activities and experienced decline in nutritional parameters measured by GA. Short-term decline in physical function after intensive induction for older patients with AML has been reported previously[34] although functional resilience may occur among longer term survivors.[35] The relationship between receipt of induction therapy on emotional health is less clear, with some studies showing lower levels of depressive symptoms and distress after treatment among older survivors.[34,35] Discrepant findings may relate to use of different measures versus varied timing of assessments or differences in patient populations.[36] Importantly, declines in physical function, mental health, and nutritional status can be addressed with supportive care if recognized. Interventions targeting maintenance of physical function during and after treatment are a particularly promising area of research.[37-39] Despite measured decrements in function by GA, global quality of life (QOL) scores were improved. Improved overall QOL after induction is consistent with results of other studies suggesting that achieving remission with improvements in symptoms has a positive effect on quality of life.[34,35,40-43] Thus,

information gained from validated GA measures is complementary to global health-related quality-of-life assessment and provides insight into specific domains such as function and nutritional status which may otherwise be missed.

This study provides additional information to support testing the role of GA to enhance risk prediction in the context of intensive AML therapy. Identifying characteristics of patients who are more or less likely to tolerate and benefit from intensive chemotherapy is critical for both treatment decision-making, trial design and supportive care.[44] A single institution study showed that physical performance and cognition (measured by the Short Physical Performance Battery and Modified Mental State Exam) are associated with worse survival among older adults treated intensively, but confirmatory multisite studies are lacking. The GA measures included in this pilot study addressed the same domains but were less comprehensive to optimize implementation (i.e. use of the Timed Up and Go and a brief 6-item cognitive screen). Our exploratory analysis was not powered to demonstrate significant associations between GA measures and survival. However, promising candidate characteristics based on estimates of effect include measures of self-reported physical function and history of falls. Functional measures have been associated with survival in hematologic malignancies in many but not all studies investigating this domain.[6,7,31,45] Data collected in this study can be used to support development of fully powered multisite studies investigating individual risk factors and risk profiles derived from GA. Larger studies will be needed to determine if more comprehensive measures of cognitive or physical function are needed to discriminate risk. Finally, the observed relationship between baseline nausea and vomiting and survival in this cohort may relate to the impact of symptom burden on outcomes which has been suggested in other studies although warrants confirmation in larger studies.[7,8]

This study has several strengths. This is the first multisite NCTN study to investigate feasibility and provide preliminary evidence for the utility of GA in the context of intensively treated patients with AML. All patients received the same therapy, limiting treatment confounding present in other studies. Collection of both GA and global quality-of-life measures provides an opportunity to better understand how to use these tools most effectively in future studies and highlights that they are not interchangeable. Finally, this study included a relatively high proportion of patients aged 70 or older (41%) which is uncommon in the literature.

This study also has limitations. The small sample size limits power to investigate the association of GA measures and treatment outcomes including overall survival and treatment-related mortality. Findings related to survival are exploratory and hypothesis generating. The sample size is inadequate to investigate which combinations of risk factors might optimally characterize fit or unfit individuals. However, the goal of this pilot was to provide preliminary data to support the feasibility of this line of investigation in larger studies. The optional nature of this ancillary study may have introduced some bias. Patients who opted not to enroll on the study may have been different in some way from those who enrolled. However, when comparing patient characteristics from those enrolled on the ancillary study to the entire clinical trial population, we see no significant differences in measurable baseline characteristics. Missing data is another limitation, with eight consented

participants missing assessments without documentation of reason for missed visits. It is reasonable to expect that those who were missing data may have differed from those who provided data. In particular, if those 6 patients missing follow-up GA data had experienced worse treatment tolerance the negative impact on functional outcomes and quality of life may be under-represented. The optional nature of the study may have contributed to missing data. Finally, patients enrolled on this study were considered fit enough for intensive chemotherapy and feasibility results may differ among populations perceived to be less fit. For example, it would be expected that the time to administer this GA among frail patients may be longer regardless of the treatment setting. Results from the GA ancillary study included in Alliance 11002 clinical trial () which enrolled less fit patients will provide this information in the future and can help identify strategies to further streamline GA for frail populations.[46] Similarly, feasibility results may differ in community practices compared to academic institutions. However, these results provide a framework to estimate resource/time allocation for patients and staff to conduct GA in the treatment evaluation of older adults, which is now guideline recommended.[47] Use of a primarily self-administered GA enhances the usability in varied settings and minimizes staff resource requirements.

In summary we have demonstrated the feasibility of performing GA in the context of an NCTN AML intensive treatment trial for older adults. Our results provide evidence to support further investigation of the use of GA in this setting and highlight the role for use of post-treatment GA to understand the impact of treatment on multiple domains of function. Larger studies can confirm these findings and inform on clinically meaningful changes for older patients. We also highlight opportunities to streamline efficiency when integrating GA into multisite trials. Next steps include validation of the utility of GA to inform risk prediction in larger multisite studies, collection of GA measures in treatment trials to characterize survivorship, and testing of interventions targeting GA-identified vulnerabilities to decrease morbidity.

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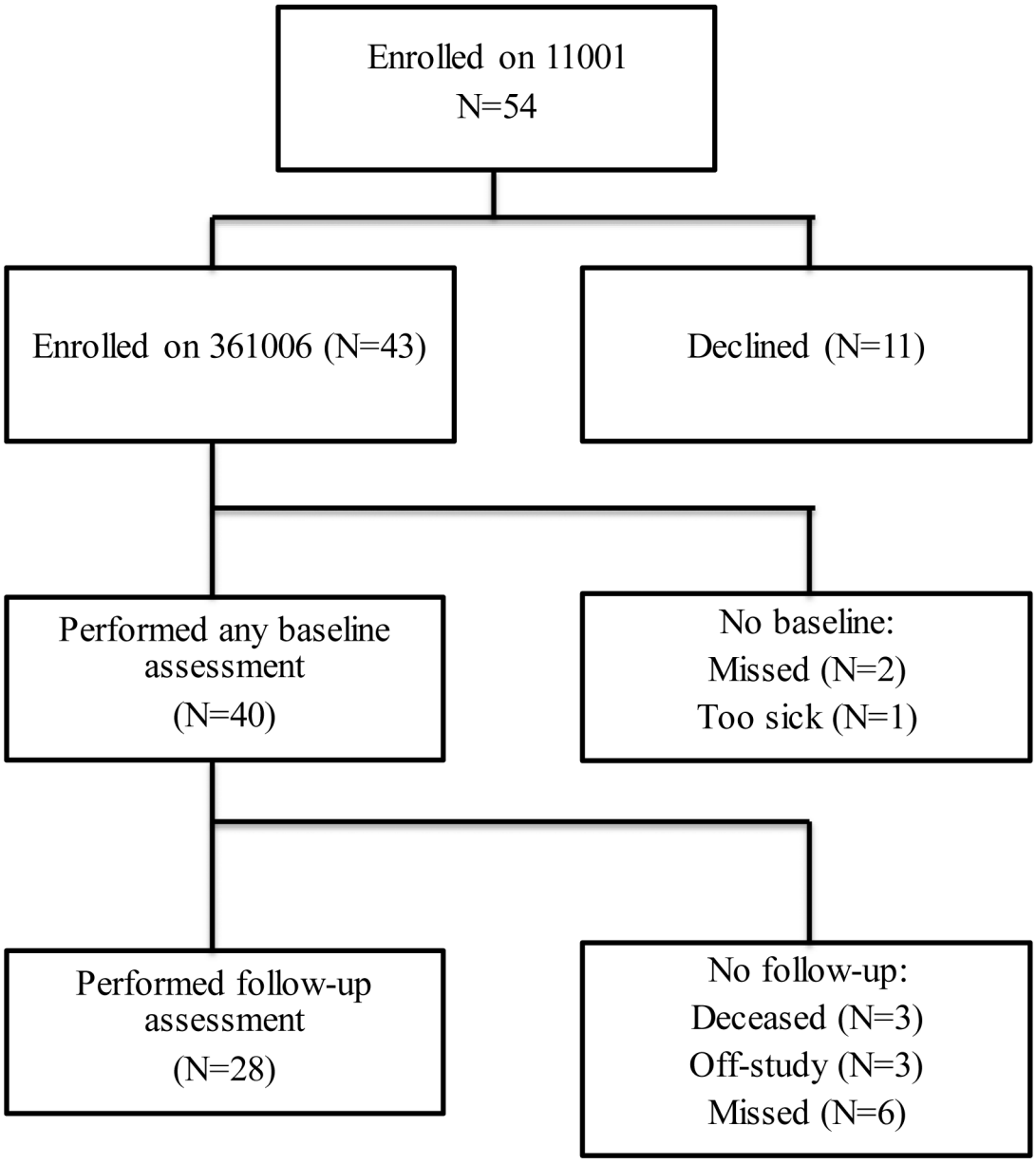

Figure 1.
Consort Diagram of enrollment and follow-up on A361006

Table 1.

Baseline characteristics of older adults with AML on A361006 (N=40)

Baseline Characteristics	**Median (range) or percent**
Demographics	
Age (yrs) median (range)	68 (61-83)
% 60-64	30
% 65-69	30
% 70-74	23
% 75-79	10
% ≥80	8
% female	40
% white	98
% non-Hispanic	85
% married	62
% with ≥ college education	39
Clinical	
FLT3 mutation	
ITD	75
TKD	25
Onset of AML	
De novo	83
Therapy-related	8
MDS-related	4
ELN classification	
CN-AML	55
Intermediate II	28
ELN Adverse	5
Unconfirmed cytogenetics	13
Bone marrow blast percentage	58 (0-96)
White blood cell count ($x10^3/mm^3$)	15 (1-344)
Lactate dehydrogenase (U/L)	516 (103-2813)
Creatinine (mg/dl)	0.9 (0.4-1.7)

Abbreviations: AML: acute myeloid leukemia; FLT3; fms related tyrosine receptor kinase 3, ITD; internal tandem duplication, TKD; tyrosine kinase domain; AML; acute myeloid leukemia, MDS; myelodysplastic syndrome, ELN; European LeukemiaNet; CN; cytogenetically normal

Table 2.

Baseline geriatric assessment and quality-of-life measures (N=40)

Domain	Measure	No. of Items	Range of Scores	Mean ± SD	Median (Range)
Functional Status	Activities of Daily Living (subscale of MOS Physical Health)	10	0-100 (higher score: better physical function)	72.1±25.8	83.3 (50-94.4)
	Instrumental Activities of Daily Living (subscale of the OARS)	7	0-14 (higher score: less need for assistance)	13.3±1.8	14 (4-14)
	*Karnofsky Self-Reported Performance Rating Scale	1	40-100 (higher score: better function)	83.2±15.1	90 (80-100)
	Karnofsky Physician-Reported Performance Rating Scale	1	10-100 (higher score: better function)	84.9±13.5	90 (50-100)
	Number of falls in last 6 months	1	Higher score, worse performance	0.4 ±1.2	0 (0-7)
	Timed up and Go (seconds)	1	Higher score: worse performance)	15.1±10	13 (5-60)
Cognition	Blessed Orientation Memory and Concentration Test (BOMC)	6	0-28 (score≥11 indicates impairment)	3.1±3.0	2 (0-12)
Comorbidity	Physician Health Section Survey (subscale of the OARS)	13	0-39 (higher score: greater comorbidity)	3.2±3.1	2.5 (0-16)
	HCT-CI	17	0-29 (higher score: greater comorbidity)	1.8±1.9	1.0 (0-7)
Medications	*Number of medications	1		4.5±3.7	4.0 (0-13)
Psychological State	Mental Health Inventory-17	17	0-100 (higher score: better mental health)	56.4±4.0	56.5 (49.4-67.1)
Social Activity	MOS Social Activity Survey	4	0-100 (higher score: better social activity)	60.3±21.8	62.5 (6.3-93.8)
Social Support	MOS Social Support Survey: Emotional Information and Tangible Subscales	12	0-100 (higher score: better social support)	83.5±16.4	92.3 (15.4-92.3)
Nutrition	*Percent unintentional weight loss in last 6 months	1		−1.9±11.7	−1.9 (−53.8-21.7)
Global Quality of life	EORTC QLQ C30 Global	30	0-100 (higher score: better QOL)	46.8±30.7	50 (0-100)

Abbreviations: MOS=Medical Outcomes Survey; OARS=Older American Resources and Services; HCT-CI=Hematopoietic cell transplantation comorbidity index; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30; QOL=quality of life

*Represents score for number of subjects completing this assessment: Patient reported KPS, N=37; Time up and go, N =35; number of falls, N = 36; number of medications, N = 33; percent weight loss, N=36.

Table 3.

Change in geriatric assessment and global quality of life after induction (N=28)

Measures	Baseline (mean±SD)	Follow-up (mean±SD)	Mean change from baseline±SD	P-value
Activities of Daily Living (subscale of MOS Physical Health)	69.5±27.8	60.5±26.6	−9.0±33.3	0.13
Instrumental Activities of Daily Living (subscale of the OARS)	13.4±1.1	12.3±2.3	−1.1±2.0	0.002
*Karnofsky Self-Reported Performance Rating Scale	81.9±15.9	82.6±17.9	0.7±21.3	0.66
*Karnofsky Physician-Reported Performance Rating Scale	82.8±13.1	84.8±9.6	2.0±13.2	0.52
*No. of falls in last 6 months	0.2±0.5	0.2±0.5	0±0.4	1.0
*Timed Up and Go (seconds)	13.5±4.3	12.1±3.9	−1.4±3.7	0.06
*Blessed Orientation Memory and Concentration Test (BOMC)	4.0 ±3.2	3.2±4.2	−0.6±3.6	0.18
*Physician Health Section Survey (subscale of the OARS)	3.4±3.5	3.7±4.6	0.3±5.0	0.80
*HCT-CI	1.9 (1.8)	1.7 (1.6)	−0.2±1.2	0.51
*Number of medications	4.0±3.4	4.4±3.6	0.4±3.7	0.5
Mental Health Inventory-17	56.1±3.4	54.2±3.2	−1.9±4.3	0.04
MOS Social Activity Survey	62.3±22.1	42.4±23.1	−19.9±24.7	0.0002
MOS Social Support Survey: Emotional Information and Tangible Subscales	94.3±10.5	91.7±15.2	−2.4±13.5	0.63
*Body Mass Index	29.9±5.5	28.1±4.8	−1.8±1.8	<0.001
*Percent unintentional weight loss in last 6 months	−2.7±12.5	−8.2±13.4	−5.6±17.3	0.03
*EORTC QLQ C30	47.8±29.8	67.9±18.8	20.2±29.4	0.001

Abbreviations: MOS=Medical Outcomes Survey; OARS=Older American Resources and Services; HCT-CI=Hematopoietic cell transplantation comorbidity index; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30; QOL=quality of life, KPS=Karnofsky performance status

*Represents score for number of subjects completing this assessment: Patient reported KPS, N=27; Physician KPS, N=25; number of falls, N = 25; Time up and go, N =23; Blessed Orientation Memory Concentration Test, N=23, physical health survey, N=27, HCT-CI, N=25, number of medications, N = 21; body mass index, N= 25, percent weight loss, N=24.

Table 4.

Univariate association between baseline geriatric assessment measures and mortality

Measure	Median Score Cut-point (N)	Hazard Ratio for Mortality (95% Confidence Interval)
Activities of Daily Living (subscale of MOS Physical Health)	≤83.3 (18)	1.6 (0.75-3.4)
	>83.3 (21)	Reference
Instrumental Activities of Daily Living (subscale of the OARS)	<14 (10)	1.7 (0.75-3.7)
	≥ 14 (29)	Reference
Number of falls in last 6 months	≥1 (8)	2.02 (0.87-4.69)
	<1 (28)	Reference
Karnofsky Self-Reported Performance Rating Scale	<90 (18)	0.8 (0.4-1.7)
	≥90 (19)	Reference
Karnofsky Physician-Reported Performance Rating Scale	<90 (15)	0.7 (0.32-1.6)
	≥90 (24)	Reference
Timed up and Go (seconds)	≤13 (17)	0.7 (0.32-1.53)
	≥ 13 (22)	Reference
Blessed Orientation Memory and Concentration Test (BOMC)	≤2 (24)	0.8 (0.4-1.7)
	> 2 (15)	Reference
Physician Health Section Survey (subscale of the OARS)	≤2.5 (19)	0.9 (0.43-1.9)
	>2.5 (19)	Reference
HCT-CI	≤1 (24)	1.23 (0.6-2.7)
	>1 (15)	Reference
Number of medications	≤4 (21)	0.8 (0.3-1.8)
	>4 (12)	Reference
Mental Health Inventory-17	<56.5 (24)	0.7 (0.3-1.4)
	≥ 56.5 (15)	Reference
MOS Social Activity Survey	≤62.5 (22)	0.7 (0.3-1.4)
	>62.5 (17)	Reference
MOS Social Support Survey	≤92.3 (17)	0.8 (0.4-1.6)
	>92.3 (22)	Reference
EORTC QLQ C30 Global	≤50 (21)	0.8 (0.3-1.7)
	>50 (16)	Reference

Abbreviations: MOS=Medical Outcomes Survey; OARS=Older American Resources and Services; HCT-CI=Hematopoietic cell transplantation comorbidity index; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30; QOL=quality of life

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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ORIGINAL RESEARCH

A prospective cohort study on the safety of checkpoint inhibitors in older cancer patients — the ELDERS study

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Objective: Older cancer patients are underrepresented in the pivotal trials of checkpoint inhibitors (CPIs). This study aimed to investigate the impact of an ageing immune system on CPI-related toxicity and provide evidence for the role of geriatric assessments with CPI.

Methods: The ELDERS study is a prospective observational study with two cohorts: older (70+ years of age) and younger (<70 years of age). Patients with advanced/metastatic non-small-cell lung cancer or melanoma starting single-agent CPI were eligible. The older cohort was assessed for frailty with Geriatric-8 (G8) screening, which when positive (<15 points) was followed by a holistic set of geriatric assessments. Primary endpoint was the incidence of grade 3-5 immune-related adverse events (irAEs).

Results: One hundred and forty patients were enrolled with 43% being pretreated and pembrolizumab represented 92% of treatments on study. The older cohort had a significantly higher comorbidity burden ($P < 0.001$) and polypharmacy ($P = 0.004$). While 50% of older patients had a positive G8 screening, 60% on this frail subgroup had a performance status score of 0 or 1. There was no significant difference in the incidence of irAEs grade 3-5 between older and younger cohorts (18.6% versus 12.9%; odds ratio 1.55, confidence interval 95% 0.61-3.89; $P = 0.353$). Exposure to systemic steroids due to irAEs was numerically longer for older patients (22 versus 8 weeks; $P = 0.208$). A positive G8 screening predicted hospital admissions ($P = 0.031$) and risk of death ($P = 0.01$).

Conclusions: The use of CPI in older patients was not associated with more high-grade toxicity. The G8 screening identified a subgroup with higher risk of AEs and its implementation should be considered in the context of CPI.

Key words: immunotherapy, cancer, toxicity, elderly, ELDERS, G8

INTRODUCTION

Cancer is predominantly a disease of older people[1,2] and it is estimated that 55% of new cases are diagnosed in people aged 65+ years.[3] Older cancer patients are, however, a heterogeneous group and assessing risk—benefit for certain therapeutic strategies can be particularly challenging. Chronological age is often inadequate to reflect functional organ reserves, treatment tolerability and prognosis. Therefore, the incorporation of comprehensive geriatric assessments (CGAs) in oncology is widely advocated.

A CGA is a two-step process with a multidimensional set of geriatric assessments followed by tailored multidisciplinary interventions to revert or optimise the problems identified. The geriatric assessments include mobility, physical status, nutritional status, psychocognitive status, socioeconomic status, functional capacity for daily life activities, comorbidity burden and polypharmacy.[4] Ultimately, a CGA has the potential to improve patients' fitness, quality of life, estimate prognosis and risk of treatment toxicity.[5]

In order to identify vulnerable/frail cancer patients who may benefit from a CGA, screening tools such as the Geriatric-8 (G8) have been developed. This screening tool has developed for cancer patients aged 70+ years and consists of eight questions/assessments.[6,7]

Immunotherapy with checkpoint inhibitors (CPIs) is revolutionising cancer treatment but the age-related remodelling process of the immune system (immunosenescence)[8] may theoretically affect their efficacy and safety profile. Data on older cancer patients on CPI are encouraging but limited because this group has been under-represented in trials.[9] This is particularly obvious in non-small-cell lung

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cancer (NSCLC) where the pivotal trials enrolled patients on average 10 years younger than the median age of NSCLC diagnosis.[10] Moreover, the pivotal trials were not designed to address the role of CPI specifically in the older or frail subgroups, nor did they incorporate geriatric assessments. In fact, geriatric assessments were developed in the setting of chemotherapy and surgery, and evidence on their role in the setting of immunotherapy is lacking.

In this context, the ELDERS study is the first prospective study designed with the aim to analyse the safety of CPI in older cancer patients, while also exploring predictive factors and the role of geriatric assessments in this setting.

PATIENTS AND METHODS

Study design

The ELDERS study was a prospective observational study with two age cohorts (1:1): older (aged 70+ years) and younger (aged <70 years). The study recruited patients with advanced/metastatic NSCLC or malignant melanoma. Those identified as eligible by their oncology teams to start single-agent CPI in any treatment line were eligible for this study. All single-agent CPIs were allowed but combination regimens were excluded. The primary endpoint was the incidence of grade 3-5 immune-related adverse events (irAEs). Secondary endpoints included investigating predictive factors for safety outcomes and the role of geriatric assessments with CPIs. Patients were recruited consecutively until each age cohort was full between October 2016 and December 2017 at The Christie NHS Foundation Trust (Manchester). Patients stopped the study due to (i) completing 12 months on study; (ii) consent withdrawal; (iii) CPI discontinuation for disease progression or (iv) death.

The study protocol was approved in the United Kingdom by the National Research Ethics Committee (ref 16/NW/0459) and sponsored by the University of Manchester. All patients provided written informed consent.

Study procedures and assessments

The safety data were collected in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.[11] The study-specific assessments were completed at baseline and at 3-monthly reviews (up to 4). Comorbidity and polypharmacy (5 concomitant medications) were assessed for all patients.[12] The Cumulative Illness Rating Scale adapted for Geriatrics (CIRS-G) measured the comorbidities by organ system.[13] Geriatric assessments were performed in the older cohort at baseline and repeated at each review. These were based primarily on the G8 screening tool. A positive G8 screening (<15 points) triggered a set of holistic geriatric assessments (which were then repeated at each subsequent review).[7] This set of assessments was performed by trained oncologists and nurses and consisted on[14] (i) Beers criteria for potentially inappropriate medications; (ii) Katz and Lawton—Brody scales for functional role on daily life activities; (iii) Holden scale and assessment on recent falls for mobility; (iv) Mini-Nutritional Assessment for nutrition status; (v) Mini-Mental State Examination for cognition; (vi) Geriatric Depression Scale-15 for psychological status; and (vii) questions on support network and living arrangements for social evaluation.

The study did not include geriatric interventions. Any relevant results were communicated to the treating oncologist and, when appropriate, referrals were made to the primary care physician/community services.

Statistical considerations and analysis

The reported incidence of grade 3-5 irAEs with single-agent CPI varies between 10% and 25%.[10,15-19] This study hypothesised that CPIs are associated with more grade 3-5 irAEs in older patients and defined that an increase of >15% compared with the younger group was clinically significant. A sample size of 140 patients (70 per group) was required to detect a significantly higher incidence from 10% in the younger group to 26% in the older group with an alpha level of 0.05 and 70% power (1-beta), while accounting for two possible study withdrawals.

Patients were evaluable for all study analysis from start of CPI throughout the active study period (up to 12 months from enrolment). Predictive factors for key safety outcomes (incidence of grade 3-5 irAEs, hospital admission and hotline use) along with prognostic factors for risk of death were explored considering disease and patient characteristics (such as data from geriatric assessments). Descriptive and inferential statistical analysis were performed including univariable and multivariable analyses. Several statistical tests were used to explore correlations according to the type of variable. For all the statistical tests, a two-sided *P*-value was used and <0.05 indicated statistical significance.

RESULTS

A total of 140 patients were eligible and successfully enrolled. Sixteen patients were ineligible after registration because a combination regimen was started ($n = 11$), the treatment plan was cancelled ($n = 4$) or due to early stage disease ($n = 1$). The median follow-up time was 6.3 months (8.5 and 5.9 months for the older and younger cohorts, respectively; $P = 0.398$). Fifty-two patients (37%) completed the planned 12 months on study. For those who stopped the study earlier, a majority (85%) stopped due to disease progression with CPI being discontinued. Consequently, while all 140 patients completed the baseline assessment, completion of the 3-monthly clinical reviews (up to 4) reduced over time. In the older cohort, 77%, 54%, 46% and 39% of patients completed the first, second, third and fourth reviews, respectively. In the younger cohort, 64%, 47%, 40% and 36% of patients completed the first, second, third and fourth reviews, respectively.

Patient characteristics

The older cohort had a significantly higher incidence of polypharmacy ($P = 0.004$) and comorbidity burden

Table 1. Baseline patient and disease characteristics

	Older cohort (n = 70)	Younger cohort (n = 70)	P value
Age			
Median (range), years	75 (70-91)	62 (43-69)	<0.001
Male, *n* (%)	41 (58.6)	44 (62.9)	0.604
Female, *n* (%)	29 (41.4)	26 (37.1)	
Performance status			
0, *n* (%)	18 (25.7)	26 (37.2)	0.166
1, *n* (%)	33 (47.1)	33 (47.1)	
2, *n* (%)	19 (27.2)	11 (15.7)	
Median (range)	25.8 (17.2-40.7)	25.2 (18.0-43.6)	0.612
Comorbidity (CIRS-G/CIRS)			
Total score, median (range)	11 (2-22)	7 (0-18)	<0.001
Any grade 3 or 4, *n* (%)	54 (77.1)	39 (55.7)	0.008
Median (range)	5 (1-14)	4 (0-14)	0.007
Polypharmacy (5), *n* (%)	43 (61.4)	26 (37.1)	0.004
Type of cancer			
Melanoma, *n* (%)	33 (47.1)	31 (44.3)	0.734
NSCLC, *n* (%)	37 (52.9)	39 (55.7)	
III, *n* (%)	11 (15.7)	5 (7.1)	0.279
IV M1a, *n* (%)	16 (22.9)	17 (24.3)	
IV M1b-c, *n* (%)	43 (61.4)	48 (68.6)	
Number of metastatic organ sites			
Median (range)	2 (0-6)	2 (0-6)	0.999
3, *n* (%)	17 (24.3)	18 (25.7)	0.845
Present, *n* (%)	4 (5.7)	10 (14.3)	0.091
LDH			
Median (range)	466 (268-2829)	463 (145-2062)	0.848
Above normal range, *n* (%)	9 (12.9)	13 (18.6)	0.353
Pembrolizumab, *n* (%)	66 (94.3)	63 (90.0)	0.784
Ipilimumab, *n* (%)	2 (2.9)	4 (5.8)	
Nivolumab, *n* (%)	1 (1.4)	1 (1.4)	
Atezolizumab, *n* (%)	0 (0.0)	1 (1.4)	
Durvalumab, *n* (%)	1 (1.4)	1 (1.4)	
Line of systemic treatment			
First, *n* (%)	43 (61.4)	37 (52.9)	0.593
Second, *n* (%)	24 (34.3)	28 (40.0)	
Third or more, *n* (%)	3 (4.3)	5 (7.1)	

CIRS(-G), Cumulative Illness Rating Scale (-Geriatrics); Con meds, concomitant medication; CPI, checkpoint inhibitor; LDH, lactate dehydrogenase; NSCLC, non-small-cell lung cancer.

[a] American Joint Committee on Cancer (AJCC) 7th edition TNM for lung cancer/melanoma.

measured by the CIRS total score ($P < 0.001$). The incidence of grade 3-4 comorbidities was significantly higher in the older cohort (77% versus 56%; $P = 0.008$). The most commonly affected systems in the younger cohort were the respiratory and vascular, whereas those in the older cohort were the vascular and musculoskeletal. All other patient and disease characteristics were similar (Table 1).

Geriatric assessments were completed in all patients in the older cohort. Thirty-five older patients (50%) had a positive G8 screening (<15 points) and all but one were identified at the baseline assessment. The exception was a patient identified at the first 3-monthly review, due to CPI toxicity which aggravated a pre-existing mild musculoskeletal autoimmune disease. The remaining patients with negative screening (fit subgroup) at baseline remained negative at the subsequent reviews. Those with a positive screening (frail subgroup) were overall older ($P = 0.056$), had a worse performance status ($P < 0.001$), a higher comorbidity burden ($P = 0.001$) and more polypharmacy ($P = 0.001$). Yet, there were no differences in cancer burden (tumour stage, number of metastatic sites and lactate dehydrogenase level). Twenty-one patients (60%) within this frail subgroup would be classed as fit if based solely on the standard performance status assessment of 0 or 1.

Following a positive geriatric screening, all these 35 patients completed a holistic set of geriatric assessments, which was repeated at each subsequent review (Figure 1). Apart from comorbidity and polypharmacy, the most commonly affected component was the capacity to perform activities of daily living in 66% of patients (Figure 2). All these patients had issues performing instrumental activities of daily living, such as shopping and cooking, but 17% of them also reported limitations with basic activities, such as eating or going to the toilet. Considering those with at least

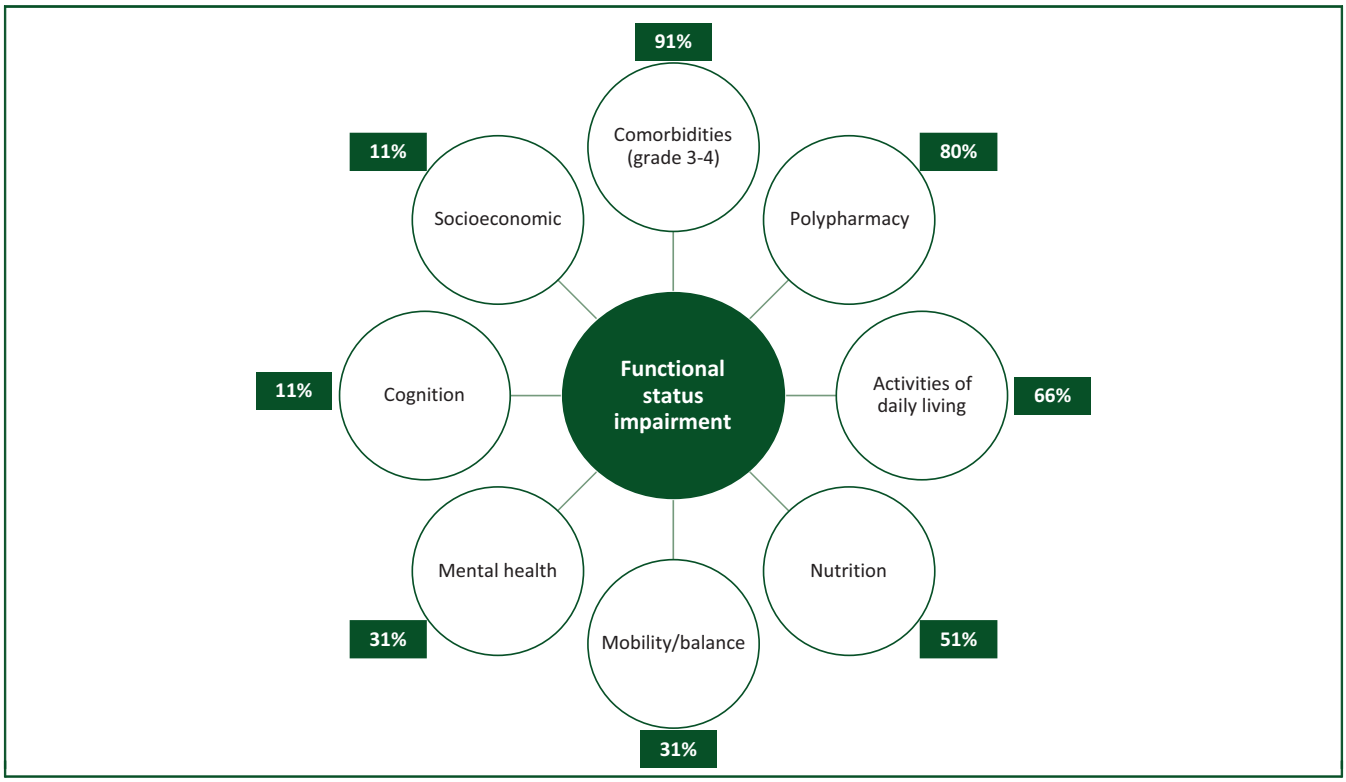

Figure 1. **Geriatric assessment components linked with functional status impairment (older cohort with a positive Geriatric-8 screening, $n = 35$).**

two sets of holistic geriatric assessments completed in two different timepoints throughout the study (23/35), a total of 19 patients (83%) were either stable or had an improvement in the affected component(s) where issues were identified. Any potential geriatric interventions directed at affected components occurred outside of the study protocol/site and their impact was not evaluable on this study.

Safety analysis

The incidence of grade 3-5 irAEs (primary endpoint) was not significantly higher in the older cohort compared with the younger cohort [18.6% versus 12.9%; odds ratio 1.55, confidence interval (CI) 95% 0.61-3.89; $P = 0.353$]. There was one case of toxic death (grade 5), which occurred in the older cohort and caused by pneumonitis. The incidence of any grade irAEs was not significantly higher in the older cohort (60% versus 51.4%; odds ratio 1.41, CI 95% 0.69-2.92; $P = 0.395$). The profile of irAEs was identical between both cohorts (Figure 2). The duration of exposure to systemic steroids (due to any grade irAEs) was numerically longer in the older cohort [median of 22 weeks (CI 95% 9.5-34.5) versus 8 weeks (CI 95% 5.3-10.7); $P = 0.208$]. No differences were observed in the incidence of non-irAEs or treatment discontinuation rate. Whereas older patients had a numerically higher use of the hotline telephone services (63% versus 50%, $P = 0.125$), the hospital admission rates were similar and, in most cases, due to non-irAEs (Table 2).

Considering the entire study population, no patient-related factors (age, performance status, body mass index, comorbidity burden and polypharmacy) or cancer burden factors (TNM stage, lactate dehydrogenase level and number of metastatic sites) were predictive for key safety outcomes (incidence of irAE grade 3-5, hospital admissions and hotline use) in multivariate analysis. However, a higher comorbidity score and polypharmacy were associated with an increased risk of death ($P = 0.04$ and $P = 0.03$, respectively).

The role of geriatric assessments

Considering the older cohort, a positive G8 screening was a predictor for hospital admissions ($P = 0.031$) in multivariate analysis. Among those with positive screening (frail subgroup), only 32% of admissions were treatment related. The remaining admissions were due to other non-irAEs (such as infections, thrombotic events, falls, pain), whereas for those with a negative screening (fit subgroup), 58% of admissions were treatment related. A positive G8 screening was also associated with higher risk of death ($P = 0.01$). For those who completed the holistic set of geriatric assessments, no signal was identified, suggesting that one particular impaired component determined a higher risk for safety outcomes or a worse prognosis.

DISCUSSION

The ELDERS study was a negative superiority study, finding no evidence that the incidence of grade 3-5 irAEs with CPI was higher in older cancer patients. While the study was designed to identify a clinically meaningful difference in high-grade toxicity for older patients, there was a limitation in its scope at a 15% difference and in the study power to

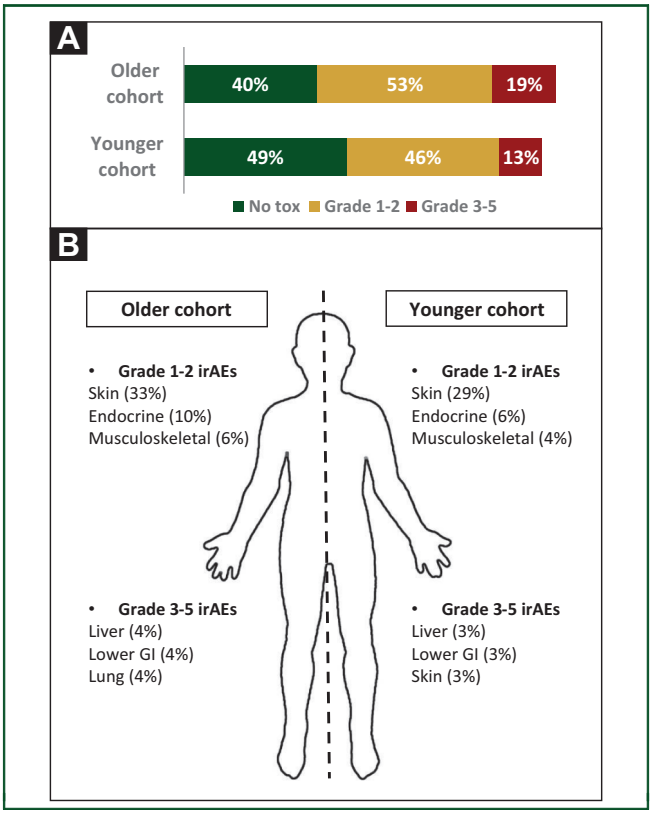

Figure 2. Distribution of immune-related toxicity.
(A) Cumulative incidence of toxicity grading per age cohort; (B) incidence of the most common toxicities per grade and age cohort. GI, gastrointestinal; irAEs, immune-related adverse events; tox, toxicity.

Table 2. Summary of safety data

	Older cohort (n = 70)	Younger cohort (n = 70)	P value
irAEs incidence			
irAEs any grade, n (%)	42 (60.0)	36 (51.4)	0.395
irAEs grade 3-5, n (%)	13 (18.6)	9 (12.9)	0.353
Toxic death, n (%)	1 (1.4)	0 (0.0)	0.999
n (%)	13 (18.6)	10 (14.3)	0.494
Immunosuppressants use (PO/IV)			
Steroids, n (%)	20 (28.6)	17 (24.3)	0.565
Median duration, weeks (range)	22 (1-32)	8 (1-52)	0.208
Infliximab, n (%)	1 (1.4)	1 (1.4)	0.999
Mycophenolate, n (%)	2 (2.9)	2 (2.9)	0.999
AEs grade 3-5, n (%)	19 (27.1)	16 (22.9)	0.558
Hospital admission			
n (%)	34 (48.6)	35 (50.0)	0.866
irAE related, n (%)	14 (20.0)	10 (14.3)	0.369
Other causes, n (%)	27 (38.6)	25 (35.7)	0.726
Hospital hotline use			
n (%)	44 (62.9)	35 (50.0)	0.125

CPI, checkpoint inhibitor; irAEs, immune-related adverse events; IV, intravenous; PO, per os.

detect it. Yet, looking beyond the incidence of high-grade toxicity, the management of immune toxicity can be more challenging in older patients. The use of systemic steroids or other immunomodulators, particularly if used for long periods, may have significant consequences. It may lead to decompensation of pre-existing diseases and iatrogenic events such as corticosteroid-induced psychosis, diabetes mellitus worsening, infections caused by atypical pathogens, myopathy and pathologic fractures. Therefore, we may underestimate the impact of irAEs particularly in the more vulnerable and older patients.

Similarly, a recent study[20] focusing on a large cohort of patients on single-agent CPI included in a pharmacovigilance registry did not find evidence of a higher risk of grade 3-5 toxicity in older patients. However, it did find a higher incidence of grade 2-4 toxicity which was driven by grade 2 toxicity and such patients had more often multiple toxicities. This highlights the risks and challenges beyond high-grade toxicity.

Chronological age has limited value to predict safety outcomes or prognosis, and standard fitness assessments, such as performance status, are less reliable to assess the functional level of older patients.[21] This highlights the importance of implementing geriatric assessments to better select older patients according to treatment tolerance and care outcomes. The fact that the study cohorts were defined exclusively based on a chronological age cut-off is debateable. However, the 70 years cut-off was defined based on the population in which the G8 screening tool was validated along with other studies implementing geriatric assessments.[7,14]

While no predictive factors for irAEs were identified in this study, a positive G8 screening (frail subgroup) was a predictor of hospital admission. However, most admissions were not CPI related, instead cancer and comorbidity related. Moreover, a positive G8 screening was prognostic for risk of death, along with comorbidity burden and polypharmacy. Ultimately, half of the older cohort screened positive but this rate was lower than anticipated, as most published evidence suggests a rate of around 70%.[7,22] This highlights a study limitation concerning a possible selection bias favouring fit patients. However, this may have been partially driven by limitations in the access to CPI, which in the case of the NSCLC population is only approved for public funding in the UK for patients with performance status score of 0 or 1.

For those patients who underwent a holistic set of geriatric assessments following a positive G8 screening, the problems identified might have been unnoticed otherwise. The most commonly identified issues were nutritional and the role function impairments on daily living activities, similarly to the published literature.[23] This study was, however, limited on the physical assessment component, where muscle strength assessments such as the handgrip and the time-up-and-go test are strongly recommended but were not implemented, because the study's assessments were mostly questionnaire based. Importantly, a formal CGA requires the implementation of both these geriatric assessments and targeted interventions. While the scope of this study was the assessment phase, several subsequent interventions were performed yet outside the study protocol via referrals to community services. Ultimately, the

study was not designed to evaluate the impact of such interventions, only the value of implementing the assessments. Moreover, the results of these assessments were not meant to influence treatment decisions, as patients were identified for the study after a treatment decision was made.

Lastly, there is no universally accepted set of geriatric assessments and interventions. Thus, it is reasonable that each hospital/practice selects those more useful and feasible to deliver within their own setting. In this study, over 95% of cases with a positive G8 screening occurred at baseline, suggesting that if there is no suspicion of frailty, then it is less likely this will develop during single-agent CPI. Therefore, focusing geriatric assessments mainly at the start of CPI may be a reasonable approach if resources are limited.

In conclusion, the use of single-agent CPI in older cancer patients was not associated with a higher incidence of high-grade immune toxicity. Nonetheless, the impact of immune toxicity, even lower grade, on this subgroup of patients may be more challenging due to their comorbidity burden and reduced organ function. Therefore, while age in itself may not play a role, the overall patient fitness does and the G8 screening tool was able to identify those vulnerable/frail older patients with a higher risk of hospital admission and higher risk of death. Its implementation for patients undergoing CPI treatment is feasible in a busy clinical practice and should be considered. This, however, should be implemented with an intention to offer holistic geriatric assessments. While not all aspects contributing to a patient's frailty may be reverted with interventions, in most cases there is room for optimisation with the support of a multidisciplinary team. Ultimately, as new combination regimens with CPI make their way into our everyday standard of care, appropriate selection of older cancer patients is paramount.

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DISCLOSURE

The authors have declared no conflicts of interest.

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original reports

Development and Validation of a Risk Tool for Predicting Severe Toxicity in Older Adults Receiving Chemotherapy for Early-Stage Breast Cancer

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abstract

PURPOSE Limited tools exist to predict the risk of chemotherapy toxicity in older adults with early-stage breast cancer.

METHODS Patients of age ≥ 65 years with stage I-III breast cancer from 16 institutions treated with neoadjuvant or adjuvant chemotherapy were prospectively evaluated for geriatric and clinical features predictive of grade 3-5 chemotherapy toxicity. Logistic regression with best-subsets selection was used to identify and incorporate independent predictors of toxicity into a model with weighted variable scoring. Model performance was evaluated using area under the ROC curve (AUC) and goodness-of-fit statistics. The model was internally and externally validated.

RESULTS In 473 patients (283 in development and 190 in validation cohort), 46% developed grade 3-5 chemotherapy toxicities. Eight independent predictors were identified (each assigned weighted points): anthracycline use (1 point), stage II or III (3 points), planned treatment duration > 3 months (4 points), abnormal liver function (3 points), low hemoglobin (3 points), falls (4 points), limited walking (3 points), and lack of social support (3 points). We calculated risk scores for each patient and defined three risk groups: low (0-5 points), intermediate (6-11 points), or high (≥ 12 points). In the development cohort, the rates of grade 3-5 chemotherapy toxicity for these three groups were 19%, 54%, and 87%, respectively ($P < .01$). In the validation cohort, the corresponding toxicity rates were 27%, 45%, and 76%. The AUC was 0.75 (95% CI, 0.70 to 0.81) in the development cohort and 0.69 (95% CI, 0.62 to 0.77) in the validation cohort. Risk groups were also associated with hospitalizations and reduced dose intensity ($P < .01$).

CONCLUSION The Cancer and Aging Research Group-Breast Cancer (CARG-BC) score was developed and validated to predict grade 3-5 chemotherapy toxicity in older adults with early-stage breast cancer.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Nearly half of the patients diagnosed with breast cancer are of age ≥ 65 years.[1] With the aging of the US population, the burden of breast cancer in older adults will continue to increase.[2,3] Although adjuvant chemotherapy improves survival in early-stage breast cancer, it is significantly underused in older patients.[4] This underutilization may be because of the increased risk of chemotherapy toxicity in older adults[5-7] and the challenges with balancing the potential benefits against the potential risks for each individual patient.[8,9]

Unlike tumor-specific genomic testing, which quantifies the potential benefits of adjuvant chemotherapy,[10] limited tools exist to predict the potential harm of chemotherapy in older adults with breast cancer. Existing measures, such as the Karnofsky performance status (KPS)[11] or Eastern Cooperative Oncology Group performance status,[12] were developed and validated in younger patients and do not reliably assess the fitness of older adults.[13,14] Incorporating variables from a geriatric assessment (GA)[15] results in more reliable tools that can better predict chemotherapy toxicity in older adults with cancer (eg, Cancer and Aging Research Group [CARG] Chemotherapy Toxicity Tool).[5-7] However, existing toxicity prediction models were developed and validated in a heterogeneous older adult population with various cancer subtypes, stages, and chemotherapy regimens. A tool that accounts for specific disease and treatment variables that are relevant for older patients with early-stage breast cancer may provide more accurate risk estimates.[16]

CONTEXT

Key Objective

To develop and validate a model that can predict grade 3-5 chemotherapy toxicity in patients of age 65 years or older with early-stage breast cancer.

Knowledge Generated

The Cancer and Aging Research Group-Breast Cancer (CARG-BC) score, derived by combining eight clinical and geriatric variables, was developed to classify older patients with early-stage breast cancer into low, intermediate, and high risk for grade 3-5 chemotherapy toxicity. The score was externally validated; demonstrated to better predict toxicity compared with prior models and physician-rated performance status; and was strongly associated with dose reductions, dose delays, early treatment discontinuation, reduced dose intensity, and hospitalizations.

Relevance

These findings may be useful to clinicians for predicting individual probability of chemotherapy toxicity and directing therapy in older adults with early-stage breast cancer. Intensifying supportive care and developing modified treatment regimens may be appropriate for subgroups identified as being vulnerable to greater toxicity.

We conducted a multicenter, prospective cohort study of older adults with early-stage breast cancer who were initiating adjuvant or neoadjuvant chemotherapy. Our main objective was to develop and validate a model to predict grade 3-5 chemotherapy toxicity in older adults with early-stage breast cancer.

METHODS

Patients

The Hurria Older PatiEnts (HOPE) with Breast Cancer Cohort Study (ClinicalTrials.gov identifier: NCT01472094) accrued patients from 16 US institutions. Eligible patients were of age ≥ 65 years, with stage I-III breast cancer of any subtype, were fluent in English, and were scheduled to receive adjuvant or neoadjuvant chemotherapy per provider discretion. Between September 2011 and May 2017, 501 patients consented to participate. The study was approved by the institutional review board at each participating institution.

Study Design and Study Cohort

This is a prospective cohort study. On the basis of our prior experience,[5,6] we included a development cohort (first 300 recruited patients) and an external validation cohort (last 201 patients). Although the validation cohort was recruited from the same institutions, they were treated during a different time period, providing evidence of external validity.[17]

Assessment of Potential Risk Factors of Chemotherapy Toxicity

Prior to the start of adjuvant or neoadjuvant chemotherapy, we collected demographic variables (age, sex, race/ethnicity, education, marital status, and household composition), clinical characteristics (tumor stage and estrogen or progesterone or human epidermal growth factor receptor 2 [HER2]-neu receptor status), laboratory data (hemoglobin, WBC count, albumin, creatinine, blood urea nitrogen, and liver function [normal defined as all liver tests are within the normal reference ranges for each institution]), planned treatment regimen and planned duration, and GA variables.[15] The GA included a healthcare provider portion and a patient portion. The healthcare provider portion consisted of physician-rated KPS,[11] Timed Up & Go test (an objective measure of physical function),[18] Blessed Orientation-Memory-Concentration test (a cognitive screening test),[19] weight, height, body mass index, and unintentional weight loss. The patient portion[5] consisted of self-reported measures of functional status,[20,21] comorbidity,[21] medications, nutrition, psychological state,[20] and social support or function[22] (Appendix Table A1, online only).

Outcomes

The primary outcome was grade 3-5 chemotherapy toxicity or adverse event (AE) as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v 4.0).[23] Patients were followed throughout the course of chemotherapy, and AEs were captured at each cycle. Subsequently, AEs were independently reviewed by two physicians (the national study principal investigator [A.H.] and site investigator) to confirm grade 3 (severe), 4 (life-threatening or disabling), and 5 (death) AEs and that the AE was chemotherapy related. For the grade 3-5 toxicity variable, we used the highest grade throughout the treatment to classify the patient. Patients could have different types of toxicities with the same highest grade; all types were reported.

Secondary outcomes included treatment modifications (dose reductions and/or delays and early treatment termination), reduced relative dose intensity (RDI, defined as the ratio of actual dose received to planned dose < 85%), and hospitalizations.

Statistical Analyses

We used descriptive analyses to summarize demographic, clinical, and GA (individual questions from validated measures in each GA domain) variables, and the incidence of grade 3-5 chemotherapy toxicities.

Model Development

In the development cohort, we used chi-squared tests to examine baseline variables in relation to toxicity. The small number of patients with missing information were not included in the analysis (n = 24). Baseline variables associated with grade 3-5 toxicity in the univariate analysis ($P < .1$) and prespecified variables deemed to be of clinical relevance (planned anthracycline, planned treatment duration, and stage) were further examined in a multivariable logistic regression model. Furthermore, we used stepwise selection to identify the most significant GA variables for inclusion in the best-subsets selection and restricted the number of variables used in the best-subsets selection to 15 variables or fewer.[24] Bayesian information criterion (BIC) was then used to identify the best size (number of variables) of the model that predicted chemotherapy toxicity. Finally, authors reviewed the top five models with the smallest BIC scores and chose the final model on the basis of the clinical relevance of the variables included. We also evaluated interactions among the selected variables, and P values $< .01$ were considered significant.

Developing the Scoring System

We assigned a point value to each variable in the final model by dividing the variable's beta coefficient by the lowest beta coefficient in the model, rounding to the nearest whole number.[5,25,26] The sum of the point values for each patient comprises the individual's risk score. We divided the group into three risk strata (low, intermediate, and high) on the basis of approximate probability of grade 3-5 toxicity $< 34\%$, 34% to $< 66\%$, and $\geq 66\%$. The difference in grade 3-5 toxicity incidence among the strata was evaluated using the chi-squared test. We evaluated the discrimination ability of the model by calculating the area under the ROC curve (AUC). The model's calibration was assessed by plotting observed and predicted probability of toxicity using LOESS smoothers and by calculating the goodness-of-fit statistics using the Hosmer-Lemeshow test.[27]

Internal Validation

The model was internally validated using 10-fold internal cross-validation and by bootstrapping to assess the extent to which the model fitting process led to an overfitting of the model.[28] To estimate how well the model would perform in new data sets, Harrell's method was used to calculate the overoptimism penalty of the predictive ability of our current model (Harrell's C),[29] which was subtracted from the AUC of the final model.

External Validation

Performance of the model was assessed in the validation cohort, the size of which allowed 80% power to detect a decrease of 0.1 in the AUC from the development cohort.[30] The AUC for the validation cohort was calculated and compared with the development cohort using the Delong nonparametric approach.[31]

Additional Analyses

Using the validation cohort, the predictive ability of the model was compared with two existing prediction tools: the CARG toxicity tool and the KPS, by comparing the AUC for the three tools using the Delong nonparametric approach.[31]

Additionally, we evaluated associations between our risk groups (categorized as low, intermediate, and high) and secondary outcomes (eg, treatment modifications, RDI, and hospitalization) using chi-squared tests. RDI was dichotomized using 85% as the cutpoint. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Among the 300 patients in the development cohort, 17 were excluded because of receiving nonstandard treatment regimens. Similarly, among the 201 patients in the validation cohort, 11 were excluded because of receiving nonstandard regimens (Appendix Fig A1, online only).

Sample Characteristics of the Development Cohort

The mean age of patients was 70.5 years (standard deviation [SD] 4.4, median 70 years, range 65-86 years), with 59% between the ages of 65 and 70 years. The majority were married (56.2%), non-Hispanic White (75.5%), lived with someone (72.1%), and had a college education or higher (72.2%). One hundred seventy-one (36.2%) had stage I, 203 (42.9%) stage II, and 99 (20.9%) stage III cancers. Nearly one quarter (23.7%) had triple-negative disease, and 27.7% had HER2-positive disease. Approximately one third of the patients received an anthracycline-based regimen (33.8%) (Appendix Table A2, online only), half of the patients had a planned duration of treatment ≤ 3 months, 17.3% received neoadjuvant chemotherapy, and 74.2% received primary prophylaxis with WBC growth factors (Table 1).

Grade 3-5 Chemotherapy Toxicities in the Development Cohort

One hundred thirty-eight patients (48.7%) developed grade 3-5 toxicities (37.5% grade 3, 11.0% grade 4, and 0.4% grade 5 [percentages reflect worst grade of toxicity experienced for patients with multiple AEs]) in the development cohort (Table 2). Grade 3-5 hematologic and nonhematologic toxicity occurred in 26.9% and 38.5% of patients, respectively. The most common grade 3-5 hematologic toxicities were anemia (13.8%), neutropenia (9.5%), and neutropenic fever (7.1%). The most common grade 3-5 nonhematologic toxicities were fatigue (11.7%), infection with normal neutrophil count (9.9%), and

TABLE 1. Distributions of Patient Demographic, Disease, and Treatment Factors in the Development and Validation Cohorts

Variable	Total (N = 473)	Development (n = 283)	Validation (n = 190)	*P*
Demographic variables				
Age (years), mean (SD)	70.5 (4.6)	70.3 (4.4)	70.8 (4.8)	.25
Median (range)	70 (65-86)	70 (65-85)	70 (65-86)	
Female no. (%)	470 (99.4%)	280 (98.9%)	190 (100%)	.28
Education no. (%)[a]				.33
≤ High school diploma	130 (27.8%)	73 (26.1%)	57 (30.3%)	
College	206 (44%)	131 (46.8%)	75 (39.9%)	
Post college	132 (28.2%)	76 (27.1%)	56 (29.8%)	
Marital status no. (%)[a]				.61
Married	264 (56.2%)	160 (57.1%)	104 (54.7%)	
Single or divorced or separated or widowed	206 (43.8%)	120 (42.9%)	86 (45.3%)	
Race or ethnicity no. (%)				.22
Non-Hispanic White	357 (75.5%)	208 (73.5%)	149 (78.4%)	
African American or Asian or Hispanics or Others	116 (24.5%)	75 (26.5%)	41 (21.6%)	
Household composition no. (%)				.41
Lives with someone	341 (72.1%)	208 (73.5%)	133 (70%)	
Lives alone	132 (27.9%)	75 (26.5%)	57 (30%)	
Employment no. (%)[a]				.47
Employed	113 (24.2%)	42 (22.5%)	71 (25.4%)	
Retired or other not working	354 (75.8%)	145 (77.5%)	209 (74.6%)	
Disease or treatment variables				
Stage no. (%)[b]				.31
I	171 (36.2%)	110 (38.9%)	61 (32.1%)	
II	203 (42.9%)	115 (40.6%)	88 (46.3%)	
III	99 (20.9%)	58 (20.5%)	41 (21.6%)	
Subtype no. (%)				.77
Triple-negative	112 (23.7%)	69 (24.4%)	43 (22.6%)	
HER2-negative or hormone receptor–positive[c]	230 (48.6%)	137 (48.4%)	93 (50.0%)	
HER2-positive or hormone receptor–positive[c]	86 (18.2%)	48 (17.0%)	38 (20.0)	
HER2-positive or ER-PR–negative	45 (9.5%)	29 (10.2%)	16 (8.4%)	
Treatment setting no. (%)				.82
Neoadjuvant	82 (17.3%)	50 (17.7%)	32 (16.8%)	
Adjuvant	391 (82.7%)	233 (82.3%)	158 (83.2%)	
Prior radiation no. (%)				.51
No	452 (95.6%)	269 (95.1%)	183 (96.3%)	
Yes	21 (4.4%)	14 (4.9%)	7 (3.7%)	
Prior chemotherapy no. (%)				.08
No	454 (96.0%)	268 (94.7%)	186 (97.9%)	
Yes	19 (4.0%)	15 (5.3%)	4 (2.1%)	
Baseline dose reduction no. (%)				.91
Standard dose	461 (97.5%)	276 (97.5%)	185 (97.4%)	
Reduced dose	12 (2.5%)	7 (2.5%)	5 (2.6%)	

(continued on following page)

TABLE 1. Distributions of Patient Demographic, Disease, and Treatment Factors in the Development and Validation Cohorts (continued)

Variable	Total (N = 473)	Development (n = 283)	Validation (n = 190)	*P*
Chemotherapy no. (%)				
Monochemotherapy	58 (12.3%)	28 (9.9%)	30 (15.8%)	.06
Polychemotherapy	415 (87.7%)	255 (90.1%)	160 (84.2%)	
Regimen no. (%)				.87
Anthracycline	160 (33.8%)	94 (33.2%)	66 (34.7%)	
Nonanthracycline	182 (38.5%)	113 (39.9%)	69 (36.3%)	
Anthracycline plus trastuzumab	25 (5.3%)	14 (4.9%)	11 (5.8%)	
Nonanthracycline plus trastuzumab	106 (22.4%)	62 (21.9%)	44 (23.2%)	
Planned duration of treatment no. (%)				.18
≤ 3 months	236 (49.9%)	134 (47.3%)	102 (53.7%)	
> 3 months	237 (50.1%)	149 (52.7%)	88 (46.3%)	
Planned WBC growth factor no. (%)				.39
No	122 (25.8%)	69 (24.4%)	53 (27.9%)	
Yes	351 (74.2%)	214 (75.6%)	137 (72.1%)	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

NOTE. *P* values comparing development and validation cohort were obtained from chi-squared or Fisher's exact test for categorical variables and *t*-test for continuous variables.

[a]Patients with missing information were not included in the calculation: five missing education, three missing marital status, and six missing employment (other not working included homemaker, unemployed, disabled, and on medical leave, etc).

[b]Stage reflects pathologic stage for patients treated in the adjuvant setting and clinical stage for patients treated in the neoadjuvant setting.

[c]Hormone receptor–positive: ER-positive or PR-negative, ER-negative or PR-positive, ER-positive or PR-positive.

dehydration (4.2%). One patient died from infection with normal absolute neutrophil count.

Development of the CARG-BC Score

The final model (Tables 3 and 4), named the Cancer and Aging Research Group-Breast Cancer (CARG-BC) score, included the following eight predictors with an AUC of 0.76: stage (II/III), planned anthracycline-based regimen, planned duration of treatment (> 3 months), abnormal liver function, anemia (hemoglobin M ≤ 13/F ≤ 12 g/dL), ≥ 1 fall in the past 6 months, limited ability to walk more than 1 mile, and lack of someone to give good advice in a crisis (Appendix Table A3, online only, with variables considered in best-subsets selection; complete univariate analysis provided in Appendix Table A4, online only). No significant interactions were found among the variables. On the basis of the bootstrapping validation, a minor model overfitting of 0.03 was identified, leaving a final adjusted AUC of 0.73. Compared with a model without the three GA variables, the addition of geriatric variables contributed significantly to the model performance (AUC 0.76 *v* 0.67, $P = .007$).

Risk scores were assigned to each variable included in the final model (Tables 3 and 4), and the CARG-BC score was calculated as the summation of points for each patient (range of potential scores 0-24). The median CARG-BC score in the developmental cohort was 7 (range 0 to 21). The model demonstrated good discrimination and calibration (Appendix Fig A2, online only), with an AUC of 0.75 (95% CI, 0.70 to 0.81) and goodness-of-fit *P* value of .49. A 10-fold internal cross-validation yielded an AUC of 0.74, indicating the model retained good discrimination. Each 1-point increase in the CARG-BC score was associated with an increased odds of AE (OR = 1.28, 95% CI, 1.19 to 1.38, $P < .001$).

The development cohort was divided into three risk groups based on the predicted probability of toxicity: low-risk (score 0-5, < 0.34), intermediate-risk (score 6-11, 0.34-< 0.66), and high-risk (score ≥ 12, ≥ 0.6). Compared with patients in the low-risk category (n = 93), the odds of experiencing chemotherapy toxicity were almost five times greater for individuals in the intermediate-risk group (n = 159; OR = 4.91, 95% CI, 2.69 to 8.96), and 28 times greater for those in the high-risk group (n = 30; OR = 28.13, 95% CI, 9.74 to 90.56); all *P* values < .001.

External Validation of the CARG-BC Score

No significant differences in demographic, disease, and treatment characteristics were noted between the development and validation cohorts (Table 1). The median CARG-BC score in the validation cohort was 8 (range 0 to 18); 59 patients (31%) were classified as low-risk, 98 (52%) as intermediate-risk, and 33 (17%) as high-risk. In the validation cohort, the association between CARG-BC score and chemotherapy toxicity was slightly attenuated but still statistically significant (27% with toxicity in the low-risk group, 45% in intermediate-risk, and 76% in high-risk; $P < 0.0001$). The AUC for the validation cohort was 0.69 (95% CI, 0.62 to 0.77), which was not significantly different from the development cohort ($P = .15$). After combining the development and validation cohorts, the overall AUC for the CARG-BC score was 0.73 (95% CI, 0.68 to 0.77).

TABLE 2. Chemotherapy-Related Grade 3-5 Toxicities in Development and Validation Cohorts

	Grade 3-5		Grade 3		Grade 4		Grade 5	
Toxicity	**Validation**	**Development**	**Validation**	**Development**	**Validation**	**Development**	**Validation**	**Development**
Hematologic and nonhematologic[a]	131 (46.3%)	85 (44.7%)	102 (36.0%)	70 (36.8%)	28 (9.9%)	13 (6.8%)	1 (0.4%)	2 (1.1%)
Hematologic	73 (25.8%)	47 (24.7%)	53 (18.7%)	38 (20.0%)	20 (7.1%)	9 (4.7%)		
ANC	25 (8.8%)	20 (10.5%)	12 (4.2%)	15 (7.9%)	13 (4.6%)	5 (2.6%)		
WBC	14 (5.0%)	6 (3.2%)	9 (3.2%)	1 (0.5%)	5 (1.8%)	5 (2.6%)		
Hemoglobin	39 (13.8%)	23 (12.1%)	39 (13.8%)	22 (11.6%)		1 (0.5%)		
Platelets	3 (1.1%)	3 (1.6%)	2 (0.7%)	2 (1.1%)	1 (0.4%)	1 (0.5%)		
Infection with abnormal ANC	19 (6.7%)	12 (6.3%)	17 (6.0%)	12 (6.3%)	2 (0.7%)			
Nonhematologic	103 (36.4%)	67 (35.3%)	93 (32.9%)	61 (32.1%)	9 (3.2%)	4 (2.1%)	1 (0.4%)	2 (1.1%)
Fatigue	32 (11.3%)	14 (7.4%)	32 (11.3%)	14 (7.4%)				
Infection with normal ANC	26 (9.2%)	16 (8.4%)	23 (8.1%)	13 (6.8%)	3 (0.7%)	3 (1.6%)	1 (0.4%)	
Dehydration	12 (4.2%)	2 (1.1%)	12 (4.2%)	2 (1.1%)				
Thrombosis or embolism	5 (1.8%)	2 (1.1%)	2 (0.7%)	2 (1.1%)	3 (1.1%)			
Hyponatremia	6 (2.1%)	1 (0.5%)	5 (1.8%)	1 (0.5%)	1 (0.4%)			
Diarrhea	9 (3.2%)	11 (5.8%)	9 (3.2%)	10 (5.3%)		1 (0.5%)		
Hypokalemia	4 (1.4%)	8 (4.2%)	3 (1.1%)	8 (4.2%)	1 (0.4%)			
Dyspnea		1 (0.5%)		1 (0.5%)				
Syncope	9 (3.2%)	4 (2.1%)	9 (3.2%)	4 (2.1%)				
Neuropathy	11 (3.9%)	8 (4.2%)	11 (3.9%)	8 (4.2%)				
Nausea	10 (3.5%)	3 (1.6%)	10 (3.5%)	3 (1.6%)				
Colonic perforation		1 (0.5%)						1 (0.5%)
Sudden death NOS		1 (0.5%)						1 (0.5%)

Abbreviations: ANC, absolute neutrophil count; NOS, not otherwise specified.

[a]The percentages for grades 3 to 5 toxicity reflect the worst grade of toxicity experienced by the individual. Since patients could have both hematologic toxicity and nonhematologic toxicity, the sum of hematologic and nonhematologic toxicities is greater than the number of all types of toxicity.

Comparison of the CARG-BC, CARG, and KPS to Predict Chemotherapy Toxicity

Using data from the validation cohort, the CARG-BC score was superior to the generalized CARG toxicity tool[5] at predicting grade 3-5 chemotherapy toxicity (AUC = 0.69 for CARG-BC score and AUC = 0.56 for generalized CARG score, $P = .004$) (Figs 1A-C). Additionally, the CARG-BC score was superior to physician-rated KPS in predicting grade 3-5 chemotherapy toxicity (AUC = 0.50 for KPS, $P < .001$) (Appendix Table A5, online only).

TABLE 3. Multivariable Predictive Model

Risk Factors	Prevalence n (%)	With Grade 3-5 toxicity n (%)	OR (95% CI)	Score
Anthracycline	106 (37%)	63 (59%)	1.28 (0.62-2.67)	1
Stage II/III	173 (61%)	95 (55%)	1.87 (1.03-3.41)	3
Planned treatment duration > 3 months	149 (53%)	87 (58%)	2.90 (1.40-6.01)	4
Abnormal liver function	29 (11%)	18 (62%)	2.28 (0.93-5.63)	3
Abnormal hemoglobin	61 (21%)	37 (61%)	2.12 (1.05-4.30)	3
Fall in the past 6 months	26 (9%)	18 (69%)	3.04 (1.13-8.24)	4
Limited in walking more than 1 mile	110 (40%)	67 (61%)	2.31 (1.30-4.15)	3
Lack of someone to give good advice in a crisis	31 (11%)	19 (61%)	2.20 (0.91-5.33)	3

Abbreviation: OR, odds ratio.

NOTE. All variables were mutually adjusted for each other in the model. Abnormal hemoglobin was defined as ≤ 12 for female and ≤ 13 for male. Abnormal liver function was defined as any liver test outside the limits of normal reference ranges of each institution.

TABLE 4. Cancer and Aging Research Group-Breast Cancer (CARG-BC) score calculator

Risk Predictor	Response	Score
Breast cancer stage	II or III	3
	I	0
Planned use of anthracyclines	Yes	1
	No	0
Planned treatment duration	> 3 months (12 weeks)	4
	≤ 3 months (12 weeks)	0
Hemoglobin	≤ 12 g/dL (female)	3
	≤ 13 g/dL (male)	
	> 12 g/dL (female)	
	> 13 g/dL (male)	0
Liver function	Abnormal LFTs, outside reference range	3
	Normal LFTs, within reference range	0
How many times have you fallen in the last 6 months?	≥ 1	4
	0	0
Does your health limit you in walking more than 1 mile?	Somewhat or very limited	3
	Not limited at all	0
How often is someone available to give you good advice about a crisis?	None, little, or some of the time	3
	Most or all of the time	0
	Total score:	

Abbreviation: LFTs, liver function tests.

Scoring: The total CARG-BC risk score is the sum of each point(s) derived from the eight independent clinical and geriatric assessment predictors of grade 3-5 chemotherapy toxicity in patients of age 65 years and older with early-stage breast cancer. Each patient's total CARG-BC score can then be classified into three risk groups: low (0-5 points), intermediate (6-11 points), or high (≥ 12 points)

Association Between the CARG-BC Score and Secondary Outcomes

Among the 473 patients in the combined development and validation cohorts, 24% required an unplanned dose reduction during therapy, 26% had a dose delay, and 24% had early discontinuation of therapy. Compared with patients in the low-risk group, those in intermediate-risk and high-risk groups were more likely to have unplanned dose reduction, dose delay, and early discontinuation of therapy (all P values $< .001$). Twenty-five percent of patients received $< 85\%$ of the ideal chemotherapy regimen (RDI), and 23% of patients were hospitalized during treatment. Patients in the intermediate- and high-risk

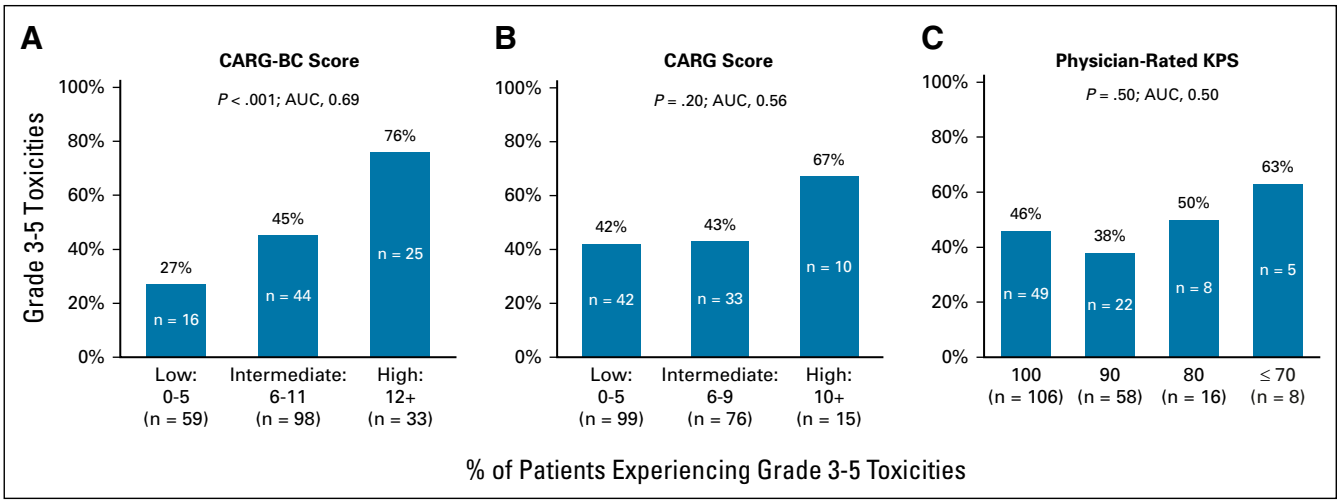

FIG 1. Association of CARG-BC score (A) with grade 3-5 chemotherapy toxicity, compared with general CARG toxicity tool (B) and physician-rated KPS (C) in the validation cohort. KPS, Karnofsky performance status. Abbreviations: CARG-BC, Cancer and Aging Research Group-Breast Cancer score; CARG, Cancer and Aging Research Group; and KPS, Karnofsky Performance Status as rated by the physician.

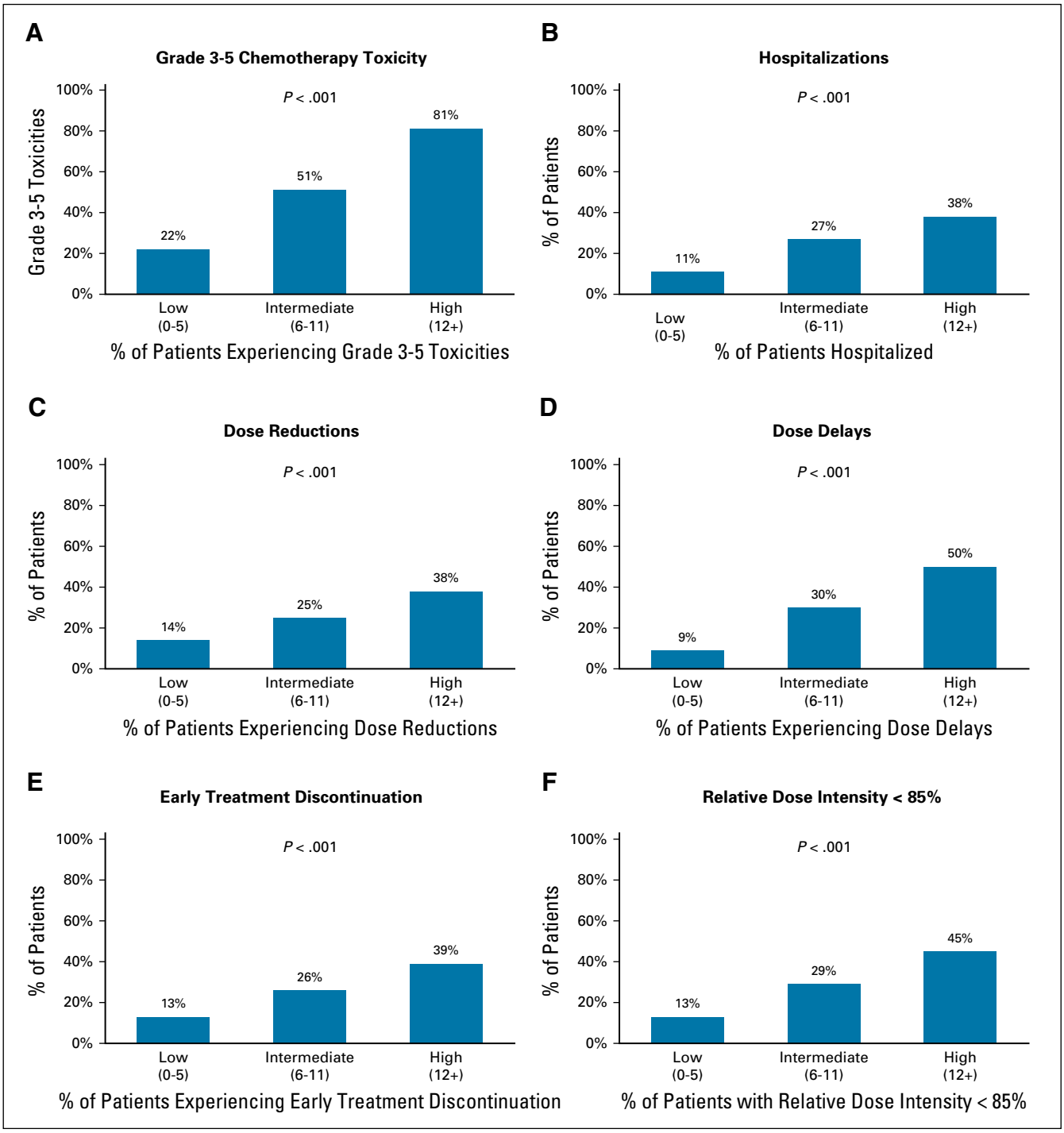

FIG 2. Association of the CARG-BC score with the proportion of patients observed to have grade 3-5 chemotherapy toxicity (A), hospitalizations (B), dose reductions (C), dose delays (D), early treatment discontinuation (E), and reduced relative dose intensity (F) as observed in the overall cohort.

groups were more likely to have received reduced RDI and were more likely to be hospitalized, compared with those in the low-risk group ($P < .001$ for both) (Figs 2A-F).

DISCUSSION

Our study demonstrates that the CARG-BC score, derived by combining eight clinical and geriatric variables, accurately classified patients of age 65 years and older with early-stage breast cancer into low-, intermediate-, and high-risk for grade 3-5 chemotherapy toxicity. The score was also validated, demonstrated to outperform the CARG toxicity risk score and KPS, and shown to be strongly associated with treatment modifications (dose reductions, dose delays, and early treatment discontinuation), reduced RDI, and hospitalizations.

This study has several important implications. First, the CARG-BC score fills a critical knowledge gap in estimating the risk of chemotherapy toxicity in the large population of older patients with early-stage breast cancer. The decision to pursue adjuvant or neoadjuvant chemotherapy for early-stage breast cancer is often a complex one for older adults. Many individuals have high-risk disease for which chemotherapy would be indicated to reduce the risk of disease recurrence. However, the development of severe chemotherapy toxicity can compromise an older adult's ability to complete the course of chemotherapy, possibly reducing the potential benefit of treatment. The CARG-BC score was found to be associated with unplanned modifications in treatment with dose reductions, dose delays, or early termination of treatment. Although data in older patients on the impact of RDI are limited, prior studies suggest that patients receiving an RDI $< 85\%$ experience poorer relapse-free survival,[32,33] and one quarter of patients on the current study received an RDI $< 85\%$. Although this score should not be used as the only factor in deciding whether to administer and/or alter the dose or schedule of chemotherapy, the CARG-BC score can be used to facilitate this complex decision-making process, along with clinical judgment and patient preferences.

Second, the CARG-BC score is significantly better at predicting toxicity than KPS, adding to the evidence demonstrating that performance status is less useful for older adults with cancer.[5,13] The CARG-BC model is also superior to the generalized CARG toxicity tool. Anemia, falls, limited mobility, and social factors were common predictors of grade 3-5 chemotherapy toxicity identified in both CARG-BC and CARG models. These results are reassuring, given that these variables assess prevalent geriatric-related deficits and are highly predictive of poor outcomes in the general older adult population. However, other variables, including cancer stage, regimen, planned treatment duration, and liver function were important predictors in this study and thus were included in CARG-BC model. Differences between these models suggest that for each specific cancer type, predictive models may have different variables that predict toxicity. Further research should investigate how best to optimize toxicity prediction tools for specific cancer types.

Third, this study underscores the value of integrating geriatric principles in routine oncology practice. Among the eight variables in our final model, three GA variables were found to significantly influence the model's predictive ability, contributing to significant improvement in the model performance. Two of the GA measures included in the CARG-BC are related to functional status: falls history and ability to walk more than 1 mile. It is well-established that functional status predicts morbidity and mortality in older adults across a variety of noncancer settings,[34,35] and falls have been strongly associated with vulnerability in older adults with cancer.[36] Through the GA, we also identified limited social support, in the form of a lack of someone to give good advice in a "crisis" from the social support survey, as a predictor of chemotherapy toxicity. Limited social support has previously been associated with increased risk of mortality after a diagnosis of breast cancer.[37] Limited social support may influence a patient's timeliness in recognizing symptoms and notifying the healthcare team of difficulties with chemotherapy, potentially delaying interventions that may minimize toxicities.

This study has limitations. One limitation of this analysis is that we examined grade 3-5 chemotherapy-related toxicities throughout the entire treatment period rather than within a defined time window. Hence, patients who had more cycles of treatment might have had a longer at-risk period. However, selecting a specific time window to assess toxicity would make it difficult to interpret the clinical significance of the model and was not used in prior risk predictive models.[5-7] Another limitation is that our population was highly educated, with 72.2% having a college education or higher, and results may be less representative of patients with lower educational status. Also, only a limited number of males were enrolled, and no inferences on a sex effect can be made. Furthermore, although the CARG-BC was validated in a separate cohort of patients, these patients were accrued from the same institutions as the development cohort. While this is an established method for validation,[17] further validation in a more diverse population should be considered in the future. Finally, the CARG-BC model does rely on self-report data, including physical function assessment, although prior studies have demonstrated correlation between patient-reported and objective physical assessment measures.[38,39]

In conclusion, we developed and validated a risk score based on eight clinical and geriatric factors that predict grade 3-5 chemotherapy toxicity in older adults with early-stage breast cancer. The risk score was also strongly associated with dose reductions, dose delays, reduced dose intensity, and hospitalizations. These findings may be useful to clinicians for predicting individual probability of chemotherapy toxicity and directing therapy, to researchers for designing and interpreting clinical trials, and to policymakers for allocating future resources for new strategies to mitigate the risk of chemotherapy toxicity.[40,41]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Development and Validation of a Risk Tool for Predicting Severe Toxicity in Older Adults Receiving Chemotherapy for Early-Stage Breast Cancer

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No potential conflicts of interest were reported.

APPENDIX

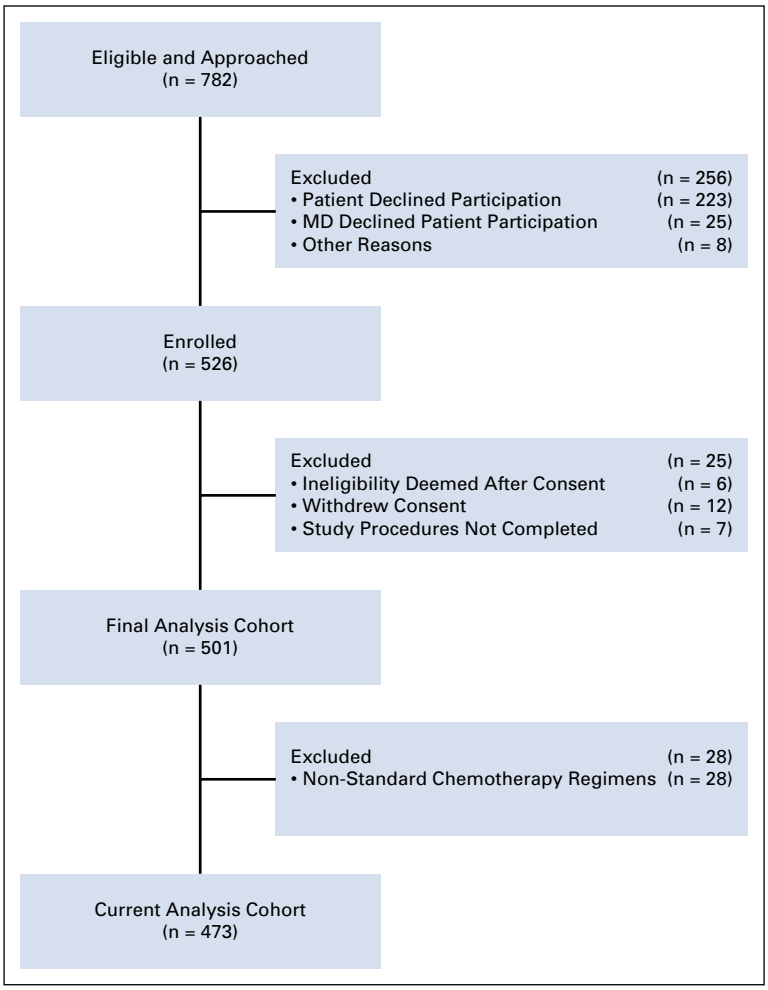

FIG A1. CONSORT diagram.

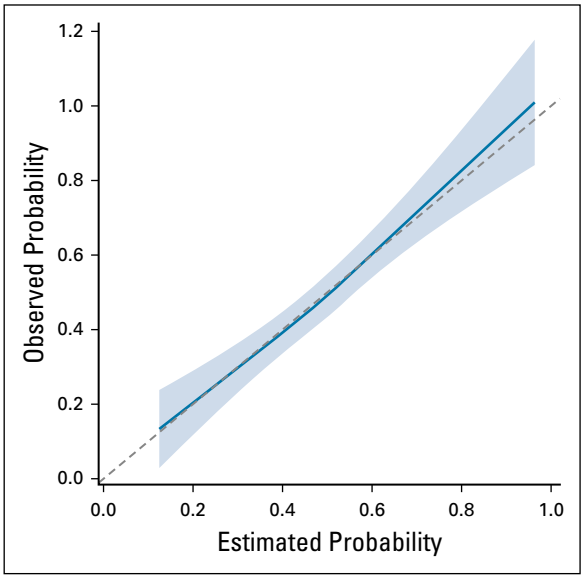

FIG A2. Calibration plot for the development cohort.

TABLE A1. Geriatric Assessment Domains, Assessment Tools, and Results

Domain	Measures	Description	Mean (SD)	Median (Range)
Functional status	Activities of daily living (medical outcomes study [MOS] subscale)	Measures limitations in physical function activities, ranging from bathing and dressing to running	79.0 (23.07)	85 (0-100)
	Instrumental activities of daily Living (older American resources and services [OARS] subscale)	Measures ability to complete activities required to maintain independence, ranging from making telephone calls to money management	13.5 (1.25)	14 (2-14)
	Karnofsky performance status (self-reported)	Global scale used quantify patient function from "normal" to "severely disabled," as determined by the patient	92.3 (11.66)	100 (40-100)
	Karnofsky performance status (physician-reported)	Global scale used quantify patient function from "normal" to "dead," as determined by the physician	93.5 (9.25)	100 (40-100)
	Timed "Up and Go" (TUG)	Time it takes for individual to stand up, walk 10 feet, return to chair and sit back down	11.5 (5.75)	10.3 (4.4-82)
	Number of falls in last 6 months	Number of times a fall occurred in the last 6 months	% with 0 falls 88.7%	% with 1 + falls 11.3%
Comorbidity	Physician health scale (OARS subscale)	Assesses the presence or absence of 13 comorbid conditions and effect of the illness on daily activities	2.4 (1.78)	2 (0-11)
Psychological state	Mental health inventory	Evaluates the level of depression and anxiety experienced in the last month	80.6 (14.81)	84.7 (10.6-100)
Social activity	MOS social activity survey	Measures the level of physical or emotional interference experienced with social activities	67.6 (18.52)	78 (− 100)
Social support	MOS social support: Emotional/informational subscale	Overall Evaluates the self-reported availability of emotional/informational social support	86.3 (18.34) 87.1 (18.88)	93.8 (0-100) 96.9 (0-100)
	MOS social support: tangible subscale	Evaluates the self-reported availability of tangible/physical social support	84.4 (21.86)	93.8 (0-100)
Nutrition	Body Mass Index	Weight (kg)/height $(m)^2$	29.8 (5.96)	29.1 (18.0-56.2)
	Percent unintentional weight loss in last 6 months	(Unintentional weight lost in last 6 months/ baseline body weight) × 100	% with ≤ 5% weight loss 92.8%	% with > 5% weight loss 7.2%
Cognition	Blessed orientation memory concentration test (BOMC)	Cognitive assessment, score 11 or greater may reveal signs of cognitive impairment	% with < 11 98.7%	% with ≥11 1.3%

TABLE A2. List of Adjuvant/Neoadjuvant Chemotherapy Regimens

Regimen	Development Cohort	Validation Cohort	Overall
Non-HER2 Regimens			
Anthracycline-based	94 (33.2%)	66 (34.7%)	160 (33.8%)
Taxane-based	97 (34.3%)	63 (33.2%)	160 (33.8%)
CMF	16 (5.7%)	6 (3.2%)	22 (4.7%)
HER2-directed Regimens			
Anthracycline-based with HER2 targeted therapy	23 (8.1%)	11 (5.8%)	34 (7.2%)
Taxane-based with HER2 targeted therapy	51 (18.0%)	44 (23.1%)	95 (20.1%)
CMF with HER2 targeted therapy	2 (0.7%)	0 (0.0%)	2 (0.4%)

Abbreviations: CMF, cyclophosphamide, methotrexate, fluorouracil; HER2, human epidermal growth factor receptor 2; HER2-targeted therapies included trastuzumab ± pertuzumab.

TABLE A3. Disease, Treatment, Labs and GA Variables included in Best-Subsets Selection: Development Cohort

	Grade 3-5 Toxicities			
	No (n = 152)	**Yes (n = 131)**	**OR (95% CI)**	***P***
Disease/treatment				
Stage, no. (row %)				
I	74 (67.3%)	36 (32.7%)	1.00	
II/III	78 (45.1%)	95 (54.9%)	2.50 (1.52 to 4.12)	< .001
Anthracycline, no. (row %)				
No	109 (61.6%)	68 (38.4%)	1.00	
Yes	43 (40.6%)	63 (59.4%)	2.34 (1.44 to 3.84)	< .001
Duration of treatment, no. (row %)				
≤ 3 mo	90 (67.2%)	44 (32.8%)		
> 3 mo	62 (41.6%)	87 (58.4%)	2.87 (1.77 to 4.67)	< .001
Labs				
Liver function, no. (row %)				
Normal	135 (54.9%)	111 (45.1%)	1.00	
Abnormal	11 (37.9%)	18 (62.1%)	1.99 (0.90 to 4.39)	.09
Hemoglobin (g/dL), No. (row %)				
Normal (M > 13/F > 12)	128 (57.7%)	94 (42.3%)	1.00	
Low (M ≤ 13/F ≤ 12)	24 (39.3%)	37 (60.7%)	2.10 (1.18 to 3.74)	.01
Creatinine clearance (Cockcroft), no. (row %)				
≥ 55	117 (57.4%)	87 (42.7%)	1.00	
< 55	32 (43.2%)	42 (56.8%)	1.7 (1.03 to 3.02)	.04
GA variables				
BMI (kg/m^2), no. (row %)				
< 30	96 (58.5%)	68 (41.5%)	1.00	
≥ 30	56 (47.1%)	63 (52.9%)	1.59(0.99 to 2.56)	.06
No. of comorbidities, no. (row %)				
< 4	130 (56.5%)	100 (43.5%)	1.00	
≥ 4	22 (41.5%)	31 (58.5%)	1.83 (1.00 to 3.36)	.05
Eyesight, no. (row %)				
Excellent	63 (62.4%)	38 (37.6%)	1.00	
Good/fair/poor	88 (48.9%)	92 (51.1%)	1.73 (1.05 to 2.85)	.03
Fall in the past 6 months, no. (row %)				
No	143 (56.1%)	112 (43.9%)	1.00	
Yes	8 (30.8%)	18 (69.2%)	2.87 (1.21 to 6.85)	.02
IADL housework, no. (row %)				
No assistance	133 (56.6%)	102 (43.4%)	1.00	
Requires assistance	19 (39.6%)	29 (60.4%)	1.99 (106 to 3.75)	.03
MOS-ADL: moderate activities, no. (row %)				
Not limited at all	123 (60.3%)	81 (39.7%)	1.00	
Limited	27 (36%)	48 (64%)	2.70 (1.56 to 4.67)	< .001
MOS ADL: limited in walking more than a mile, no. (row %)				
Not limited at all	106 (63.1%)	62 (36.9%)	1.00	
Limited	43 (39.1%)	67 (60.9%)	2.66 (1.62 to 4.37)	< .001

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TABLE A3. Disease, Treatment, Labs and GA Variables included in Best-Subsets Selection: Development Cohort (continued)

	Grade 3-5 Toxicities			
	No (n = 152)	Yes (n = 131)	OR (95% CI)	*P*
Social support				
Someone to give you good advice in a crisis, no. (row %)				
Most/all of the time	138 (55.6%)	110 (44.4%)	1.00	
None/s little/some of the time	12 (38.7%)	19 (61.3%)	1.99 (0.92 to 4.27)	.08
Psychological state (MHI)				
Has your daily life been full of things that were interesting to you, no. (row %)				
All/most/a good bit of the time	131 (57.2%)	98 (42.8%)	1.00	
Some/a little/none of the time	18 (39.1%)	28 (60.9%)	2.08 (1.09 to 3.97)	.03

Abbreviations: ADL, Activities of Daily Living scale; BMI, body mass index; IADL, Instrumental Activities of Daily Living scale; MOS, medical outcomes study; OR, odds ratio.

[a]Patients with missing values were excluded from analysis: eight missing liver function, one missing eyesight information, two missing fall, four missing moderate activity, five missing limited in walking a mile, four missing social support advice, eight missing MHI daily life full of interesting things. Hemoglobin: Normal was defined as $>$ 12 for female and $>$ 13 for male.

TABLE A4. Univariate Analysis

	Grade 3-5 Chemotherapy Toxicity			
	No (N = 152)	Yes (N = 131)	Total (N = 283)	*P*
Demographic factors				
Categorical age				.16
65-70	95 (57.2%)	71 (42.8%)	166	
71 +	57 (48.7%)	60 (51.3%)	117	
Sex				.65
Female	150 (53.6%)	130 (46.4%)	280	
Male	2 (66.7%)	1 (33.3%)	3	
Education				.79
≤ High school diploma	38 (52.1%)	35 (47.9%)	73	
College	68 (51.9%)	63 (48.1%)	131	
Post college	43 (56.6%)	33 (43.4%)	76	
Missing	3	0	3	
Married				.49
Single/divorced/separated/widowed	61 (50.8%)	59 (49.2%)	120	
Married	88 (55%)	72 (45%)	160	
Missing	3	0	3	
Household composition				.85
Live with someone	111 (53.4%)	97 (46.6%)	208	
Live alone	41 (54.7%)	34 (45.3%)	75	
Race/ethnicity				.49
Non-Hispanic White	112 (53.8%)	96 (46.2%)	208	
Black	26 (59.1%)	18 (40.9%)	44	
Asian/Hispanic/others	14 (45.2%)	17 (54.8%)	31	

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TABLE A4. Univariate Analysis (continued)

	Grade 3-5 Chemotherapy Toxicity			
	No (N = 152)	**Yes (N = 131)**	**Total (N = 283)**	***P***
Disease factors				
Stage				.0003
I	74 (67.3%)	36 (32.7%)	110	
II/II	78 (45.1%)	95 (54.9%)	173	
Subtype				.52
Triple negative	39 (56.5%)	30 (43.5%)	69	
HER2 −/hormone receptor +***	73 (53.3%)	64 (46.7%)	137	
HER2 +/hormone receptor +***	22 (45.8%)	26 (54.2%)	48	
HER2 +/ER-PR −	18 (62.1%)	11 (37.9%)	29	
Baseline dose reduction				.56
No	149 (54.0%)	127 (46.0%)	276	
Yes	3 (42.9%)	4 (57.1%)	7	
Planned white cell growth factor				.17
No	42 (60.9%)	27 (39.1%)	69	
Yes	110 (51.4%)	104 (48.6%)	214	
Planned duration of treatment				< .0001
≤ 3 mo	90 (67.2%)	44 (32.8%)	134	
> 3 mo	62 (41.6%)	87 (58.4%)	149	
Treatment setting				.23
Neoadjuvant	23 (46.0%)	27 (54.0%)	50	
Adjuvant	129 (55.4%)	104 (44.6%)	233	
Chemotherapy				.0003
Polychemotherapy	24 (85.7%)	4 (14.3%)	28	
Monochemotherapy	128 (50.2%)	127 (49.8%)	255	
Regimen				.0026
Anthracylcine	41 (43.6%)	53 (56.4%)	94	
Non-anthracycline	70 (61.9%)	43 (38.1%)	113	
Anthracycline + Trastuzumab	3 (21.4%)	11 (78.6%)	14	
Non-anthracycline +trastuzumab	38 (61.3%)	24 (38.7%)	62	
Planned anthracycline				.0006
No	109 (61.6%)	68 (38.4%)	177	
Yes	43 (40.6%)	63 (59.4%)	106	
Planned trastuzumab				.98
No	110 (53.7%)	95 (46.3%)	205	
Yes	42 (53.8%)	36 (46.2%)	78	
Planned taxane				.67
No	15 (57.7%)	11 (42.3%)	26	
Yes	137 (53.3%)	120 (46.7%)	257	
Planned carboplatin				.07
No	141 (55.5%)	113 (44.5%)	254	
Yes	11 (37.9%)	18 (62.1%)	29	

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TABLE A4. Univariate Analysis (continued)

	Grade 3-5 Chemotherapy Toxicity			
	No (N = 152)	**Yes (N = 131)**	**Total (N = 283)**	***P***
Planned cyclophosphamide				.19
No	35 (61.4%)	22 (38.6%)	57	
Yes	117 (51.8%)	109 (48.2%)	226	
Prior radiation				.42
No	143 (53.2%)	126 (46.8%)	269	
Yes	9 (64.3%)	5 (35.7%)	14	
Prior chemotherapy				.99
No	138 (53.5%)	120 (46.5%)	258	
Yes	8 (53.3%)	7 (46.7%)	15	
Missing	6	4	10	
LAB values				
Hemoglobin (g/dL)				.01
Normal (M > 13/F > 12)	128 (57.7%)	94 (42.3%)	222	
Low (M ≤ 13/F ≤ 12)	24 (39.3%)	37 (60.7%)	61	
White blood cell (cmm)				.12
≤ 11,000	123 (51.7%)	115 (48.3%)	238	
> 11,000	29 (64.4%)	16 (35.6%)	45	
Albumin (g/100mL)				.27
> 3.6	132 (54.1%)	112 (45.9%)	244	
≤ 3.6	5 (38.5%)	8 (61.5%)	13	
Missing	15	11	26	
Liver function				.08
Normal	135 (54.9%)	111 (45.1%)	246	
Abnormal	11 (37.9%)	18 (62.1%)	29	
Missing	6	2	8	
Creatinine clearance[a]				.04
< 55	32 (43.2%)	42 (56.8%)	74	
≥ 55	117 (57.4%)	87 (42.6%)	204	
Missing	3	2	5	
BUN (mg/dL)				.68
≤ 22	111 (52.1%)	102 (47.9%)	213	
> 22	32 (55.2%)	26 (44.8%)	58	
Missing	9	3	12	
IADL				
IADL housework				.03
No assistance	133 (56.6%)	102 (43.4%)	235	
Requires assistance	19 (39.6%)	29 (60.4%)	48	
IADL meal preparation				.58
No assistance	146 (54.1%)	124 (45.9%)	270	
Requires assistance	6 (46.2%)	7 (53.8%)	13	
IADL taking medication				.20
No assistance	144 (52.9%)	128 (47.1%)	272	
Requires assistance	8 (72.7%)	3 (27.3%)	11	

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TABLE A4. Univariate Analysis (continued)

	Grade 3-5 Chemotherapy Toxicity			
	No (N = 152)	Yes (N = 131)	Total (N = 283)	*P*
IADL get to places out of walking distance				.42
No assistance	141 (54.4%)	118 (45.6%)	259	
Requires assistance	11 (45.8%)	13 (54.2%)	24	
IADL handle your own money				.98
No assistance	144 (53.7%)	124 (46.3%)	268	
Requires assistance	8 (53.3%)	7 (46.7%)	15	
IADL shopping for groceries/clothes				.19
No assistance	145 (54.7%)	120 (45.3%)	265	
Requires assistance	7 (38.9%)	11 (61.1%)	18	
IADL use telephone				.23
No assistance	148 (53.2%)	130 (46.8%)	278	
Requires assistance	4 (80.0%)	1 (20.0%)	5	
MOS-ADL				
Bathing or dressing yourself				.78
Not limited at all	142 (53.6%)	123 (46.4%)	265	
Limited	8 (50.0%)	8 (50.0%)	16	
Missing	2	0	2	
Bending, kneeling, or stooping				.01
Not limited at all	108 (59%)	75 (41%)	183	
Limited	41 (42.7%)	55 (57.3%)	96	
Missing	3	1	4	
Climbing one flight of stairs				.05
Not limited at all	134 (55.8%)	106 (44.2%)	240	
Limited	16 (39.0%)	25 (61.0%)	41	
Missing	2	0	2	
MOS_ClimbingSeveralFlights2				.04
Not limited at all	105 (58.0%)	76 (42.0%)	181	
Limited	45 (45.5%)	54 (54.5%)	99	
Missing	2	1	3	
Lifting or carrying groceries				.14
Not limited at all	119 (55.9%)	94 (44.1%)	213	
Limited	30 (45.5%)	36 (54.5%)	66	
Missing	3	1	4	
Moderate activities				.0003
Not limited at all	123 (60.3%)	81 (39.7%)	204	
Limited	27 (36.0%)	48 (64.0%)	75	
Missing	2	2	4	
Vigorous activities				.04
Not limited at all	51 (63.0%)	30 (37.0%)	81	
Limited	96 (49.2%)	99 (50.8%)	195	
Missing	5	2	7	
Walking more than a mile				.0001

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TABLE A4. Univariate Analysis (continued)

	Grade 3-5 Chemotherapy Toxicity			
	No (N = 152)	**Yes (N = 131)**	**Total (N = 283)**	***P***
Not limited at all	106 (63.1%)	62 (36.9%)	168	
Limited	43 (39.1%)	67 (60.9%)	110	
Missing	3	2	5	
Walking one block				.43
Not limited at all	134 (54.3%)	113 (45.7%)	247	
Limited	16 (47.1%)	18 (52.9%)	34	
Missing	2	0	2	
Walking several blocks				.002
Not limited at all	125 (58.7%)	88 (41.3%)	213	
Limited	25 (37.3%)	42 (62.7%)	67	
Missing	2	1	3	
KPS, fall, timed up and go				
MD KPS				.06
< 90	16 (40.0%)	24 (60.0%)	40	
≥ 90	136 (56.0%)	107 (44.0%)	243	
Self-rated KPS				.10
< 90	17 (41.5%)	24 (58.5%)	41	
≥ 90	131 (55.3%)	106 (44.7%)	237	
Missing	4	1	5	
Fall				.01
No	143 (56.1%)	112 (43.9%)	255	
Yes	8 (30.8%)	18 (69.2%)	26	
Missing	1	1	2	
Timed up and go (seconds)				.79
< 10	56 (54.9%)	46 (45.1%)	102	
≥ 10	90 (53.3%)	79 (46.7%)	169	
Missing	6	6	12	
Social support				
Someone to help if you were confined to bed				.35
None/a little/some of the time	30 (48.4%)	32 (51.6%)	62	
Most/all of the time	120 (55.0%)	98 (45.0%)	218	
Missing	2	1	3	
Someone you can count on to listen to you when you need to talk				.57
None/a little/some of the time	12 (48.0%)	13 (52.0%)	25	
Most/all of the time	138 (53.9%)	118 (46.1%)	256	
Missing	2	0	2	
Someone to give you good advice about a crisis				.07
None/a little/some of the time	12 (38.7%)	19 (61.3%)	31	
Most/all of the time	138 (55.6%)	110 (44.4%)	248	
Missing	2	2	4	
Someone to take you to the doctor if needed				.29
None/a little/some of the time	6 (40.0%)	9 (60.0%)	15	

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TABLE A4. Univariate Analysis (continued)

	Grade 3-5 Chemotherapy Toxicity			
	No (N = 152)	Yes (N = 131)	Total (N = 283)	*P*
Most/all of the time	144 (54.1%)	122 (45.9%)	266	
Missing	2	0	2	
Someone to give you information to help you understand a situation				.15
None/a little/some of the time	9 (39.1%)	14 (60.9%)	23	
Most/all of the time	141 (54.9%)	116 (45.1%)	257	
Missing	2	1	3	
Someone to confide in or talk to about yourself or your problem				.17
None/a little/some of the time	11 (40.7%)	16 (59.3%)	27	
Most/all of the time	137 (54.6%)	114 (45.4%)	251	
Missing	4	1	5	
Someone to prepare your meals if you were unable to do it yourself				.59
None/a little/some of the time	22 (50.0%)	22 (50.0%)	44	
Most/all of the time	128 (54.5%)	107 (45.5%)	235	
Missing	2	2	4	
Someone whose advice you really want				.17
None/a little/some of the time	18 (43.9%)	23 (56.1%)	41	
Most/all of the time	131 (55.5%)	105 (44.5%)	236	
Missing	3	3	6	
Someone to help you with daily chores if you were sick				.93
None/a little/some of the time	27 (54.0%)	23 (46.0%)	50	
Most/all of the time	122 (53.3%)	107 (46.7%)	229	
Missing	3	1	4	
Someone to share your most private worries and fears with				.50
None/a little/some of the time	19 (48.7%)	20 (51.3%)	39	
Most/all of the time	131 (54.6%)	109 (45.4%)	240	
Missing	2	2	4	
Someone to turn to for suggestions about how to deal with a personal problem				.16
None/a little/some of the time	14 (42.4%)	19 (57.6%)	33	
Most/all of the time	136 (55.3%)	110 (44.7%)	246	
Missing	2	2	4	
Someone who understands your problems				.63
None/a little/Some of the time	16 (50.0%)	16 (50.0%)	32	
Most/all of the time	134 (54.5%)	112 (45.5%)	246	
Missing	2	3	5	
Social activity				
Physical health or emotional problems interfered with your social activities				.39
All/most/some of the time	34 (49.3%)	35 (50.7%)	69	
A little/none of the time	117 (55.2%)	95 (44.8%)	212	
Missing	1	1	2	
Social activity change during the past 6 months				.84
Same	96 (53.0%)	85 (47.0%)	181	

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TABLE A4. Univariate Analysis (continued)

	Grade 3-5 Chemotherapy Toxicity			
	No (N = 152)	**Yes (N = 131)**	**Total (N = 283)**	***P***
Less	47 (54.0%)	40 (46.0%)	87	
More	8 (61.5%)	5 (38.5%)	13	
Missing	1	1	2	
Social activities comparing to similar age				.24
Same	57 (48.3%)	61 (51.7%)	118	
Less	19 (55.9%)	15 (44.1%)	34	
More	75 (59.1%)	52 (40.9%)	127	
Missing	1	3	4	
Extent of interference				.17
Moderate/quite a bit/extremely	25 (45.5%)	30 (54.5%)	55	
Slightly/not at all	126 (55.8%)	100 (44.2%)	226	
Missing	1	1	2	
Cognition				
BOMC				.87
< 11	149 (54%)	127 (46%)	276	
≥ 11	2 (50%)	2 (50%)	4	
Missing	1	2	3	
Nutrition				
BMI, kg/m^2				.06
< 30	96 (58.5%)	68 (41.5%)	164	
30 +	56 (47.1%)	63 (52.9%)	119	
BSA, m^2				.62
< 2	122 (54.5%)	102 (45.5%)	224	
≥ 2	30 (50.9%)	29 (49.1%)	59	
Unintentional weight loss				.52
No or < 5%	141 (53.2%)	124 (46.8%)	265	
≥ 5%	11 (61.1%)	7 (38.9%)	18	
Comorbidity				
Number of comorbidity				.05
< 4	130 (56.5%)	100 (43.5%)	230	
≥ 4	22 (41.5%)	31 (58.5%)	53	
Comorbidity cancer				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	109 (50.7%)	106 (49.3%)	215	.45
Cancer	19 (73.1%)	7 (26.9%)	26	.19
Comorbidity arthritis				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	55 (54.5%)	46 (45.5%)	101	.77
Arthritis	73 (52.1%)	67 (47.9%)	140	.57
Comorbidity glaucoma				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	118 (53.6%)	102 (46.4%)	220	.68
Glaucoma	10 (47.6%)	11 (52.4%)	21	.48

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TABLE A4. Univariate Analysis (continued)

	Grade 3-5 Chemotherapy Toxicity			
	No (N = 152)	**Yes (N = 131)**	**Total (N = 283)**	***P***
Comorbidity emphysema				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	119 (52.2%)	109 (47.8%)	228	.56
Emphysema	9 (69.2%)	4 (30.8%)	13	.44
Comorbidity HBP				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	51 (59.3%)	35 (40.7%)	86	.82
HBP	77 (49.7%)	78 (50.3%)	155	.39
Comorbidity heart				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	117 (55.5%)	94 (44.5%)	211	.84
Heart condition	11 (36.7%)	19 (63.3%)	30	.09
Comorbidity circulation				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	109 (54.8%)	90 (45.2%)	199	.78
Circulation problem	19 (45.2%)	23 (54.8%)	42	.27
Comorbidity diabetes				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	104 (54.5%)	87 (45.5%)	191	.75
Diabetes	24 (48.0%)	26 (52.0%)	50	.38
Comorbidity stomach				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	111 (56.1%)	87 (43.9%)	198	.90
Stomach problem	17 (39.5%)	26 (60.5%)	43	.11
Comorbidity osteoporosis				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	94 (49.5%)	96 (50.5%)	190	.37
Osteoporosis	34 (66.7%)	17 (33.3%)	51	.35
Comorbidity liver kidney				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	124 (53.2%)	109 (46.8%)	233	.64
Liver/kidney problem	4 (50.0%)	4.0 (50%)	8	.71
Comorbidity stroke				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	128 (54.0%)	109 (46.0%)	237	.71
Stroke	0 (0.0%)	4 (100.0%)	4	.98
Comorbidity depression				
None	24 (57.1%)	18 (42.9%)	42	ref
Other	107 (55.2%)	87 (44.8%)	194	.81
Depression	21 (44.7%)	26 (55.3%)	47	.24
Eye sight				.03
Good/fair/poor	88 (48.9%)	92 (51.1%)	180	

(continued on following page)

TABLE A4. Univariate Analysis (continued)

	Grade 3-5 Chemotherapy Toxicity			
	No (N = 152)	**Yes (N = 131)**	**Total (N = 283)**	***P***
Excellent	63 (62.4%)	38 (37.6%)	101	
Missing	1	1	2	
Hearing				.03
Good/fair/poor	81 (47.9%)	88 (52.1%)	169	
Excellent	68 (61.3%)	43 (38.7%)	111	
Missing	3	0	3	
MHI section				
Has your daily life been full of things that were interesting to you				.02
All/most/a good bit of the time	131 (57.2%)	98 (42.8%)	229	
Some/a little/none of the time	18 (39.1%)	28 (60.9%)	46	
Missing	3	5	8	
Did you feel depressed				.43
All/most/a good bit of the time	10 (45.5%)	12 (54.5%)	22	
Some/a little/none of the time	138 (54.1%)	117 (45.9%)	255	
Missing	4	2	6	
Have you felt loved and wanted				.08
All/most/a good bit of the time	142 (54.8%)	117 (45.2%)	259	
Some/a little/none of the time	6 (33.3%)	12 (66.7%)	18	
Missing	4	2	6	
Have you been a very nervous person				.93
All/most/a good bit of the time	18 (54.5%)	15 (45.5%)	33	
Some/a little/none of the time	131 (53.7%)	113 (46.3%)	244	
Missing	3	3	6	
Have you been in firm control of your behavior, thoughts, emotions, feelings				.82
All/most/a good bit of the time	135 (53.6%)	117 (46.4%)	252	
Some/a little/none of the time	14 (56.0%)	11 (44.0%)	25	
Missing	3	3	6	
Have you felt tense or high-strung				.70
All/most/a good bit of the time	21 (56.8%)	16 (43.2%)	37	
Some/a little/none of the time	128 (53.3%)	112 (46.7%)	240	
Missing	3	3	6	
Have you felt calm or peaceful				.11
All/most/a good bit of the time	115 (56.1%)	90 (43.9%)	205	
Some/a little/none of the time	33 (45.2%)	40 (54.8%)	73	
Missing	4	1	5	
Have you felt emotionally stable				.07
All/most/a good bit of the time	137 (55.7%)	109 (44.3%)	246	
Some/A little/None of the time	12 (38.7%)	19 (61.3%)	31	
Missing	3	3	6	
Have you felt downhearted and blue				.60
All/most/a good bit of the time	9 (47.4%)	10 (52.6%)	19	

(continued on following page)

TABLE A4. Univariate Analysis (continued)

	Grade 3-5 Chemotherapy Toxicity			
	No (N = 152)	Yes (N = 131)	Total (N = 283)	*P*
Some/a little/none of the time	139 (53.7%)	120 (46.3%)	259	
Missing	4	1	5	
Have you felt restless, fidgety, or impatient				.54
All/most/a good bit of the time	15 (48.4%)	16 (51.6%)	31	
Some/a little/none of the time	134 (54.3%)	113 (45.7%)	247	
Missing	3	2	5	
Have you been moody, or brooded about things				.42
All/most/a good bit of the time	7 (43.8%)	9 (56.3%)	16	
Some/a little/none of the time	140 (54.1%)	119 (45.9%)	259	
Missing	5	3	8	
Have you felt cheerful, light-hearted				.02
All/most/a good bit of the time	124 (56.9%)	94 (43.1%)	218	
Some/a little/none of the time	24 (40.0%)	36 (60.0%)	60	
Missing	4	1	5	
Have you been in low or very low spirits				.76
All/most/a good bit of the time	11 (50.0%)	11 (50.0%)	22	
Some/a little/none of the time	136 (53.3%)	119 (46.7%)	255	
Missing	5	1	6	
Were you a happy person				.91
All/most/a good bit of the time	138 (53.7%)	119 (46.3%)	257	
Some/a little/none of the time	11 (52.4%)	10 (47.6%)	21	
Missing	3	2	5	
Did you feel you had nothing to look forward to				.39
All/most/a good bit of the time	4 (40.0%)	6 (60.0%)	10	
Some/a little/none of the time	144 (53.9%)	123 (46.1%)	267	
Missing	4	2	6	
Have you felt so down in the dumps that nothing could cheer you up				.89
All/most/a good bit of the time	5 (55.6%)	4 (44.4%)	9	
Some/a little/none of the time	143 (53.2%)	126 (46.8%)	269	
Missing	4	1	5	
Have you been anxious or worried				.97
All/most/a good bit of the time	22 (53.7%)	19 (46.3%)	41	
Some/a little/none of the time	127 (53.4%)	111 (46.6%)	238	
Missing	3	1	4	

Abbreviations: ADL, Activities of Daily Living scale; BMI, body mass index; BUN, blood urea nitrogen; HER2, human epidermal growth factor receptor 2; IADL, Instrumental Activities of Daily Living scale; MOS, medical outcomes study.

[a]Creatinine clearance was calculated based on Cockcroft gault formula using adjusted body weight.

TABLE A5. Model Performance Comparison Between CARG-BC, CARG, and KPS Utilizing the Development and Validation Cohort

	CARG-BC # of Patients With Gr 3-5 Toxicity/Total # Patients With Risk Score		**CARG # of Patients With Gr 3-5 Toxicity /Total # Patients With Risk Score**		**MD KPS # of Patients With Gr 3-5 Toxicity /Total # Patients With KPS Score**	
Development cohort (n = 283)	Low	18/93	Low	55/152	100	70/156
	Intermediate	86/159	Intermediate	65/113	90	37/87
	High	27/31	High	11/18	80	16/29
					≤ 70	8/11
	P	< .001	*P*	.001	*P*	.20
	AUC	0.75	AUC	0.64	AUC	0.53
Validation cohort (n = 190)	Low	16/59	Low	42/99	100	49/106
	Intermediate	44/98	Intermediate	33/76	90	22/58
	High	25/33	High	10/15	80	8/16
					≤ 70	5/8
	P	< .001	*P*	.20	*P*	.50
	AUC	0.69	AUC	0.56	AUC	0.50

Abbreviations: AUC, area under the ROC curve; CARG-BC, Cancer and Aging Research Group-Breast Cancer; KPS, Karnofsky performance status