**Enhanced Sensitivity of EGFR Inhibitor Resistant NSCLC and Drug Tolerant Persister Cells to Chimeric Antigen Receptor (CAR)-NK Cellular Therapy**

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Patients with non-small cell lung cancer (NSCLC) harboring EGFR mutations often benefit from tyrosine kinase inhibitors (TKIs) such as osimertinib. However, the emergence of drug-tolerant persister cells (DTPCs), which eventually give rise to drug-resistant cells (DRCs), remains a therapeutic challenge. Furthermore, EGFR-TKI resistant NSCLCs are refractory to immune checkpoint inhibitors. Therefore, novel treatment strategies are urgently needed. Chimeric antigen receptors (CARs) have shown promise in augmenting the anti-tumor activity of immune effector cells. In this study, we evaluated the efficacy of CAR-based therapies for parental EGFR mutant NSCLC cells, osimertinib-resistant (OR) cells, and osimertinib DTPCs. Our findings demonstrate robust cytotoxic activity of EGFR CAR-T and CAR-NK cells against parental cells, while OR cells displayed altered sensitivities: reduced response to EGFR CAR-T and enhanced susceptibility to EGFR CAR-NK treatment. Notably, DTPCs showed increased sensitivity to both EGFR CAR-T and CAR-NK cells. Mechanistically, altered EGFR levels, epithelial-mesenchymal transition (EMT) status, increased B7-H6 (*NCR3LG1*) expression, and elevated NKG2D ligands (MICA, MICB, and ULBP1) contributed to differential responses to EGFR CAR-T and CAR-NK cells. Treatment with osimertinib elevated EGFR expression on OR cells, rendering them more responsive to EGFR-CAR therapy. Additionally, elevated TGF-β levels in EGFR-TKI-resistant cells suppressed CAR-T and CAR-NK function, which was rescued by TGF-β pathway inhibition through galunisertib or dominant-negative TGF-β receptor II (DNTGFBRII) co-expression in EGFR CAR-NK cells. Furthermore, EGFR CAR-NK cells demonstrated complete responses in HCC827 xenograft models. In an osimertinib-resistant model (H1975 OR17), EGFR CAR-NK cells significantly inhibited tumor growth as compared to control NK cells (p < 0.001). Moreover, DNTGFBRII-expressing CAR-NK cells treatment resulted in a significantly reduced tumor volume as compared to EGFR CAR-NK cells (p < 0.001). Furthermore, in H1975 osimertinib DTPC *in vivo* models, EGFR CAR-NK cells demonstrated potent efficacy either in combination with osimertinib or following osimertinib treatment. In conclusion, EGFR-directed cellular therapies, particularly EGFR CAR-NK cells, are active against drug-resistant models of EGFR mutant NSCLC and DTPCs, and that this activity is enhanced by combination with TKIs or TGF-β pathway blockade.