**Utilizing GLP-1R Agonist for Endometrial Cancer Therapy**

Vishal Chandra; Danielle Krause; Rajani Rai

Gynecologic Oncology Section, Obstetrics and Gynecology Department, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA.

**Abstract**

Endometrial cancer (EC) is the fourth most common cancer in females in the United States. Endometrioid EC is the most common subtype, arising due to excess estrogen unopposed by progesterone, and is often preceded by atypical endometrial hyperplasia (AEH/EIN). Surgery is the standard treatment for AEH/EC. While progestin therapy serves as an alternative treatment, it is accompanied by 20-40% recurrence rates. In this study, we aim to investigate the effects of GLP1-R agonists, which are widely used for diabetes and obesity treatment, against EC.

Protein and mRNA levels of the GLP1 receptor (GLP1R) were compared between the benign and EC cell lines. The efficacy of GLP-1 agonists was assessed in progesterone-resistant EC cells by cell viability assay. Progesterone activity was measured by analyzing the expression of its downstream effectors FOXO-1 and Cyclin D1. An *in vivo* xenograft mouse model (developed from progesterone-resistant EC cells) fed on a high-fat diet was used to evaluate the efficacy of GLP1-R agonist alone and in combination with progesterone therapy. The tumor volume, body weight, and body fat composition were also measured.

GLP1-R mRNA and protein levels were found to be significant upregulation in EC cells compared to benign cells. GLP1-R agonist significantly decreased EC cell proliferation and demonstrated better efficacy in combination with progesterone compared to each drug alone. GLP1-R agonist treatment downregulated cyclin D1 and upregulated FOXO-1 in a dose- and cell line-dependent manner, respectively. In a xenograft model, GLP1-R agonist treatment significantly reduced tumor volume. In addition, GLP-1 agonists significantly reduced body weight gain due to a high-fat diet and were associated with decreased body weight and fat mass. In combination with progesterone, the GLP1-R agonist significantly reduced tumor size and increased survival compared to the individual drugs and controls. In conclusion, GLP-1 agonists combined with progesterone may provide novel therapeutic alternatives for EC and may mitigate progestin-associated weight gain. However, further studies are needed to fully elucidate the mechanisms and long-term effects of GLP1-R agonist and progestin combination therapy in EC

**Acknowledgment:** This study was supported by "Specialized Programs of Research Excellence/SPOREs- Career Enhancement Program” and “Mary Kay Ash Foundation".