GLP-1 Receptor Agonist in Combination with Radiotherapy Significantly Delays Tumor Growth and Improves Overall Survival in a Murine Model of Triple Negative Breast Cancer

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Background

Triple negative breast cancer (TNBC) is a subtype of breast cancer that accounts for approximately 15-20% of all breast cancers and is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. TNBC has the poorest prognosis among all breast cancer subtypes due to its molecular heterogeneity, high proliferation rate, and ability to undergo clonal evolution after treatment with chemotherapy. Despite remarkable improvement in the treatment of TNBC with chemoimmunotherapy (KEYNOTE-522, KEYNOTE-355), 37% of early-stage patients do not survive beyond the first 5 years following surgery. In the metastatic setting, the 5-year overall survival rate is a dismal 11%, highlighting the need for more effective therapies. A significant risk factor for the development of TNBC is metabolic syndrome. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of medications approved for the treatment of type 2 diabetes mellitus and obesity that have garnered attention for their multifaceted roles beyond glycemic control, including in malignancy through modulating anti-tumor immunity and regulating signaling pathways involved in cancer cell growth and survival. Given their potential effect in breast cancer, we hypothesize that GLP-1RAs enhance the response to cytotoxic therapy, thereby delaying tumor growth and improving survival.

Methods and Materials

Female C57BL/6 mice were inoculated with syngeneic EO771 TNBC cells, a murine model commonly used to mimic human TNBC, via intramammary injection in their lower mammary fat pads. Transplanted mice were treated when tumors achieved a minimum size of 300 mm^3, at which time tumor-bearing mice were divided into the appropriate experimental cohorts with treatment groups receiving radiotherapy (RT) alone, GLP-1 receptor agonist Exendin-4 (Ex-4) alone, or radiotherapy combined with Ex-4. RT was given at a one-time dose of 16 Gy. Ex-4 was administered at a dosage of 30 nmol/kg body weight daily via IP injection. Tumor growth was quantitatively measured every 3 days throughout the studies using calipers until endpoint, defined as when the tumors reach a maximum size of 2000 mm^3. Tumor size comparisons between experimental groups were analyzed using the 2-way ANOVA (Analysis of Variance) test. All end points were evaluated utilizing the Kaplan-Meier method. Hazard ratios (HR) were estimated using the Mantel-Haenszel method. All reported 95% confidence intervals (CI) are two-sided.

Results

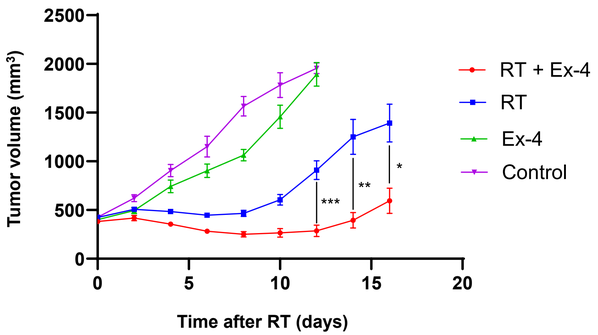


Figure 1. Quantification of tumor size after receiving RT treatment with mean and standard errors plotted. *P<0.05, **P<0.01, ***P<0.001.

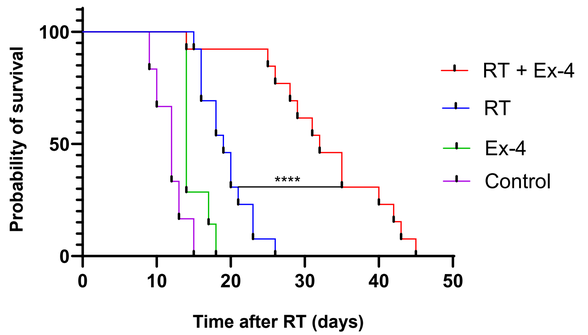


Figure 2. Survival curve for mice bearing EO771 tumors. ****P<0.0001.

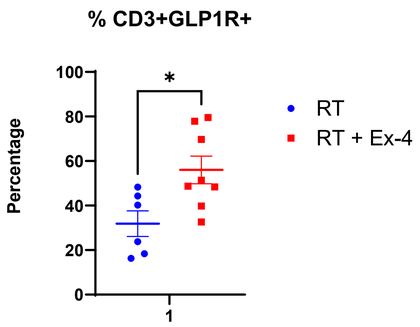


Figure 3. Percentage distribution of $CD45^+CD11b^-CD11c^-CD19^-CD3^+GLP1R^+$ cells in the tumor microenvironment at 7 days post RT treatment. *P<0.05.

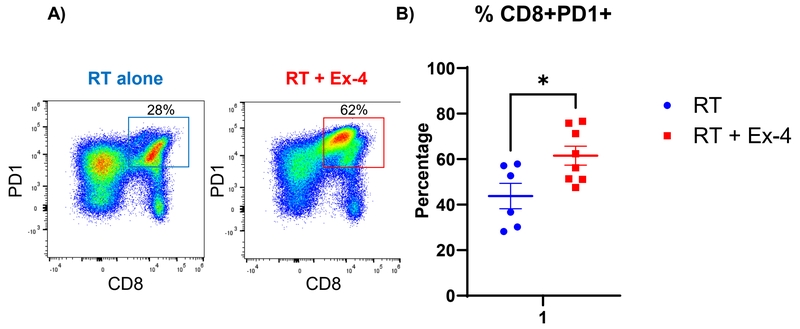


Figure 4. A) Representative flow cytometry analyses and B) Percentage distribution of $CD45^+CD11b^-CD11c^-CD19^-CD3^+CD8^+PD1^+$ cells in the tumor microenvironment at 7 days post RT treatment. *P<0.05.

Discussion

The results show that 12 days following RT, the combination of Ex-4 + RT (n = 13) significantly delayed tumor growth compared to RT alone (n = 13) (p = 0.0007). In addition, Ex-4 + RT significantly improved overall survival versus RT alone (HR 0.26, CI 0.09-0.66, p < 0.0001). The median survival of the RT cohort and Ex-4 + RT cohort were 19 days and 32 days, respectively, from the day of RT treatment. On the other hand, the median survival of the Ex-4 alone group was 14 days and that of the control group was 12 days. Thus, our findings provide compelling phenotypic evidence that GLP-1RAs synergize with cytotoxic therapy in modulating tumor biology to produce a robust anti-tumor response. Preliminary flow cytometry analyses of tumor tissue harvested from mice bearing EO771 TNBC cells at 7 days post RT treatment demonstrate an increased percentage of $CD3^+GLP1R^+$ cells and $CD8^+PD1^+$ cells in the Ex-4 + RT cohort compared to the RT cohort. These data suggest that GLP-1R signaling can potentially augment tumor infiltrating lymphocytes to promote a more immunogenic state post-radiation.

Conclusions

In summary, we demonstrate that combination GLP-1RA and radiotherapy confers a significant delay in tumor growth and an improved overall survival benefit in a murine model of TNBC. Additional immunophenotypic and functional studies are ongoing to determine the mechanism by which combination treatment affects the anti-tumor immune response.

Future Directions

Our study is an original proposal designed to answer clinically applicable questions in the field of breast cancer. To our knowledge, this project will be the first to study the mechanisms in which GLP-1RAs affect the TNBC intratumoral immune and non-immune cell composition and function. We would also like to explore the impact of combined therapy in models of metastatic disease to determine if GLP-1RAs can reduce progression to metastases. Importantly, completion of these studies will allow us to take critical initial steps toward identifying metabolism-focused therapeutic strategies to improve the treatment of this highly aggressive subtype of breast cancer. Ultimately, based on the findings of this project, we hope to design clinical trials to determine if the novel combination GLP-1RA with cytotoxic therapy leads to more robust treatment responses for the treatment of TNBC.

Contact

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