Expansion of Dendritic Cells Using FLT3 Ligand to Treat Glioblastoma: A Preclinical Study

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Introduction

Flt3L induces expansion and recruitment of plasmacytoid dendritic cells (pDCs) into the brain. By increasing antigen presentation, FLT3L agonists may enhance an immune response against glioblastoma (GBM). Previous results suggest that the antitumor response generated by FLT3 is secondary to production of interferon gamma. We studied the effect of FLT3L treatment of mice with a syngeneic GBM model.

Methods

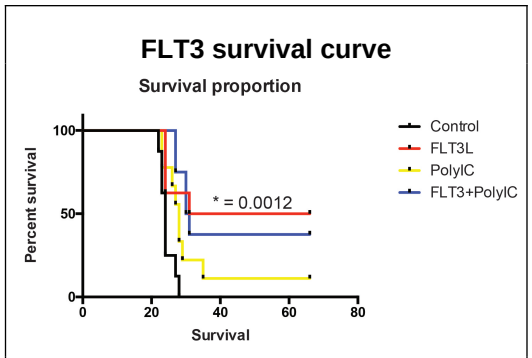
Under ACUC approval, 32 mice underwent implantation of 130,000 GL261 cells in the left striatum using a stereotactic frame. The presence of tumor was confirmed by bioluminescence imaging at day 7. Mice were randomized to 4 groups: Control, FLT3 (courtesy of Celldex) treatment, Poly IC treatment, and FLT3+Poly IC treatment. Survival was assessed using log-rank analysis and described using Kaplan-Meier curves.

Results

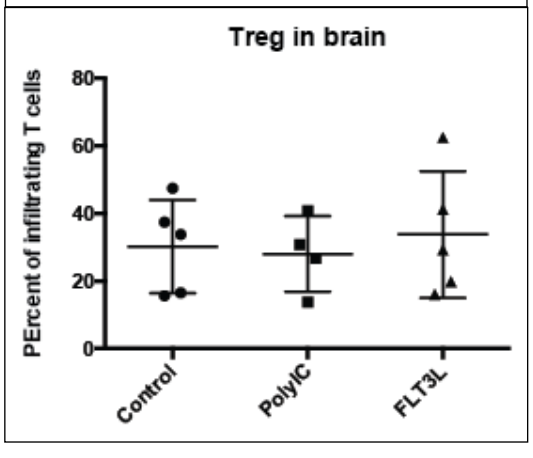
FLT3L treatment of mice resulted in 50% long-term survival of mice and improved survival compared to control groups (p=0.0012).

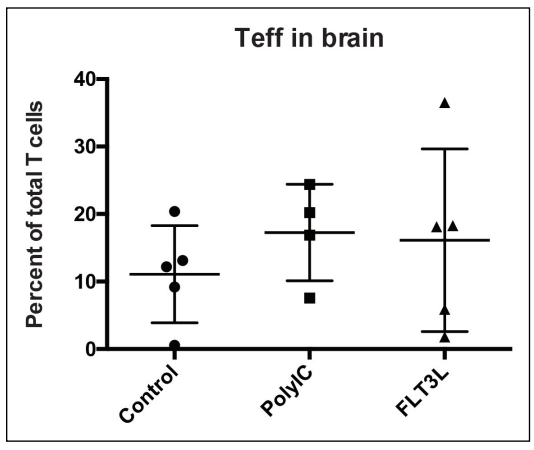
Addition of Poly IC (TLR3 agonist), did not add survival benefit.

There was no change in the prorportion of infiltrating regulatory T cells of effector T cells, although there was an increasing trend in effector T cells in the brain.



Kaplan Meier of GL261 mice treated with FLT3L and PolyIC





Conclusions

The present work suggests that an increase in antigen presentation by enhancing and recruiting dendritic cells into the brain and brain tumor may be beneficial and a potential therapeutic strategy for patients with GBM. The mechanism of this phenomenon is currently under investigation, but include increased secretion of interferon -gamma. Additionally, increased antigen presentation may aid the immune system mount a significant anti-tumor immune response. Further experiments evaluating the proportion of T cells that have been exposed to antigen are currently underway.

Learning Objectives

Evaluate the antitumor immune response after FLT3L activation of dendritic cells

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