The addition of Toca 511 and 5-FC to temozolomide improves response in a temozolomide-resistant murine glioblastoma model and correlates with Toca 511 dose

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Abstract

Toca 511 (vacinamge amiretrope), an amphotrophic retroviral replicating vector (RRV), can successfully and safely deliver a functional, optimized yeast cytosine deaminase (CD) gene to tumors. Within infected cells, CD converts 5-fluorocytosine (5-FC) to the anti-cancer drug 5-fluorouracil (5-FU). The combination of Toca 511 with oral extended release 5-FC (Toca FC), is currently being evaluated in a randomized phase III clinical trial for recurrent high grade glioma (glioblastoma (GBM) and anaplastic astrocytoma) (NCT02414165). Toco 515. Temozolomide (TMZ), in combination with radiation therapy, after surgery is the standard of care used for first-line chemotherapy treatment of patients with GBM, the most common and aggressive form of primary brain cancer. Previously, we have shown that: (1) Toca 511/5-FC treatment provides durable response in a syngeneic murine glioma model and supports anti-tumor immune memory; (2) The combination of TMZ and Toca 511/5-FC has synergistic efficacy in a TMZ-sensitive human glioma nude mouse model; (3) TMZ did not inhibit the efficacy of Toca 511/5-FC in a TMZ resistant murine glioma syngeneic model; (4) Toca 511/5-FC caused significant radiosensitization in a radiosensitive murine glioma model.

Results: To assess the interaction of TMZ with escalating doses of Toca 511 (as defined by percent of tumor transduction by RRV), an orthotopic TMZ-resistant murine glioma model, Tu-2449, was utilized. These results show that moderate levels of tumor transduction of Toca 511 (30% - 50%) with 5-FC treatment longer survival in the presence of TMZ compared with lower transduction rates (10%). Conclusion: These results demonstrate that (1) survival associates with the transduction levels of Toca 511 when combined with TMZ in the Tu-2449 orthotopic glioma model and (2) that this combination may support anti-tumor immune memory. These studies along with prior work support evaluation of the combination of Toca 511/5-FC with TMZ in patients with newly diagnosed GBM (NRG-BN006).

Introduction

Toca 511 is a retroviral replicating vector (RRV) expressing a cytosine deaminase (CD) gene. Toca 511 is selective for tumor cells. CD buds off from but does not lyse tumor cells directly. CD converts 5-FC (5-fluorocytosine) into anti-cancer drug 5-FU (5-fluorouracil). Immune system is activated selectively against the tumor.

Methods

1) Tumor cell implantation
   Tu-2449 were implanted orthotopically (Figure 1).

2) Treatment
   TMZ & 5-FC

3) Statistical analysis of blood was performed. T-test compared to baseline of treated animals (t-test, 2-tailed, unequal variance). In chart above, significance of P values is indicated by color.

Blood analyses showed:

- As TMZ concentration increased, mice became more immunosuppressed and persisted before the third week of treatment.
- TMZ contributes to hematological toxicity; whereas, 5-FC does not create additional toxicity.
- Addition of low dose TMZ (25 mg/kg) had lower effect on blood cell populations than higher doses.
- Blood collection from animals showed low levels of WBC, lymphocytes and neutrophils in line with a leukopenia phenotype.
- Platelets and hematocrit were largely unaffected by TMZ.

Conclusion

- 5-FC combined with lympho-depleting TMZ provides survival benefit at 30% and 50% Toca 511 infection.
- TMZ depletes various blood populations, including white blood cells, lymphocytes and neutrophils.
- Optimization of the immune-associated mechanism of Toca 511 & TMZ can improve survival benefit of Toca 511 infection.
- Data from this study may inform and help design new clinical development of Toca 511 and Toca FC with TMZ standard of care in GBM.

REFERENCES:

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