SITC POSTER #565

A novel long-acting interleukin-7 agonist, NT-I7, increases cytotoxic CD8+ T cells and enhances survival in mouse glioma models

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BACKGROUND

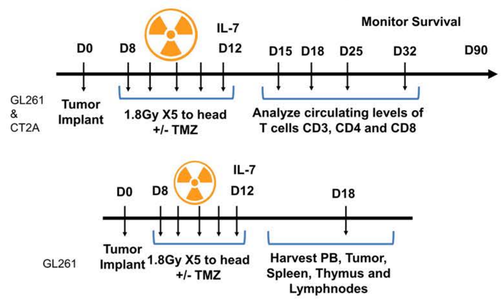
Radiation (RT) and temozolomide (TMZ), the standard of care for glioblastoma (GBM), often causes a prolonged and severe treatment-related lymphopenia (TRL) that has been proven an independent risk factor for shorter survival (1-3). Concomitant treatments designed to counteract severe TRL could increase efficacy of the SOC while decreasing serious side effects. Levels of Interleukin-7 (IL-7), a homeostatic cytokine required for the survival and proliferation of naïve and memory T cells, are inappropriately low in GBM patients with severe TRL. NT-I7 (efineptakin alfa) is a long-acting recombinant human IL-7 (rhIL-7) that supports proliferation and survival of CD4 and CD8 T cells in both humans and mice (4,5). Thus our aim was to test whether NT-I7 treatment, by rescuing the treatment-related lymphopenia, was able to increase survival in the GBM murine model.

1. Grossman et al. Clin Cancer Res (2011) 17:5473
2. Campian et al. J Neurooncol (2015) 124:307
3. Huang et al. Int J Radiat Oncol Biol Phys (2015) 92:1000
4. Lee et al. Clin Transl Sci. 2020 Apr 27. doi: 10.1111/cts.12800
5. Kim et al. Clin Transl Immunol (2020) 9:e1168

METHODS

Immunocompetent C57BL/6 mice bearing two intracranial glioma models (GL261 and CT2A) were treated with RT (1.8 Gy/day x 5 days), TMZ (33 mg/kg/day x 5 days) and/or NT-I7 (rhIL-7) (10 mg/kg on the final day of RT completion). We profiled the CD3, CD8, CD4, FOXP3 cells in peripheral blood over time. We also immunoprofiled cervical lymph nodes, bone marrow, thymus, spleen, and the tumor 6 days after NT-I7 treatment. Survival was monitored daily.

Experimental Design



ACKNOWLEDGEMENTS

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RESULTS

NT-I7 in combination with radiation significantly improves survival.

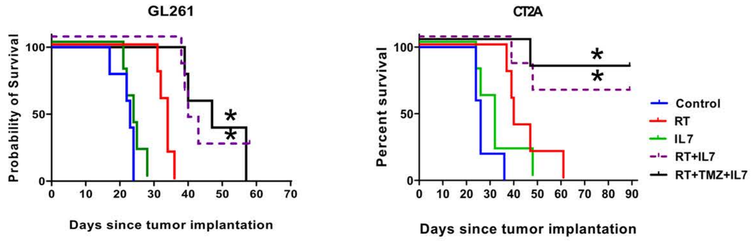

Figure 1. Median survival significantly increased in orthotopic mice (GL261 and CT2A) treated with NT-I7 (RT vs. RT+IL-7 - GL261: 40d vs 34d, p<0.0021; CT2A: 90d vs 40d, p<0.0499). RT+IL-7 was as effective as RT+TMZ+IL-7 in both GL261(40d vs 47d) and CT2A (90d vs 90d). The data are expressed as mean ± SD from 5 mice.

NT-I7 preferentially increases cytotoxic CD8+ T cells.

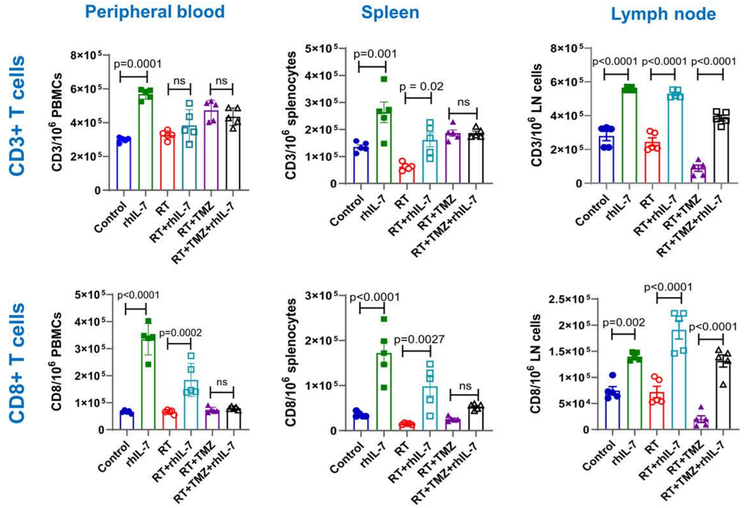

Figure 2. Orthotropic mice bearing GL261 tumors treated with NT-I7 had enhanced T cells (*CD3+)*, partially restoring the severe lymphopenia induced by radiation (upper panel). NT-I7 treatment also enhanced cytotoxic T cells (CD8+), crucial to the immune response against tumors (*lower panel*). The mice treated with NT-I7 in combination with radiation significantly increased the CD8+ T cells in peripheral blood, spleen and lymph nodes. Despite the deep lymphopenic state induced by RT/TMZ, the IL-7 in combination with RT/TMZ significantly increased the number of CD8+ T cells within the LN.

NT-I7 increases CD8+ T cells by replenishing the naïve pool within lymphoid organs.

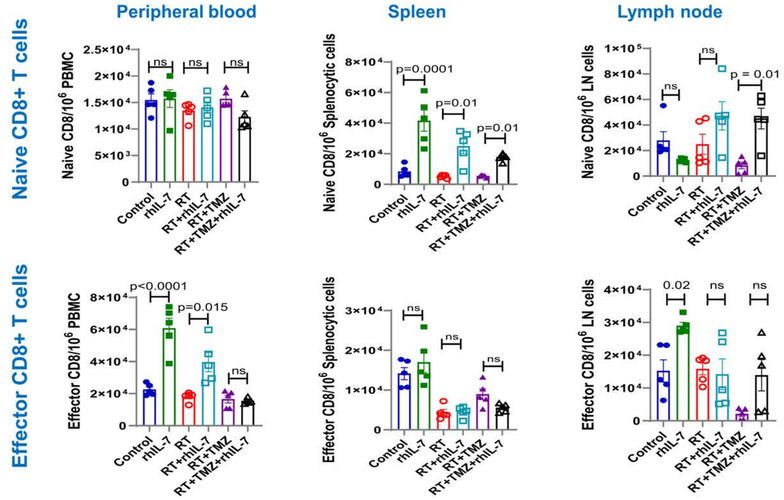

Figure 3. Orthotropic mice bearing GL261 tumors treated with NT-I7 had significantly increased the number of naïve CD8+ T cells within the spleen and lymph nodes in all combination treatments (*upper panel*) while increasing the number of circulating effector CD8+ T cells (*lower panel*)

NT-I7 increase the CD8+ T cells but decreases the T_{reg} cells in tumor.

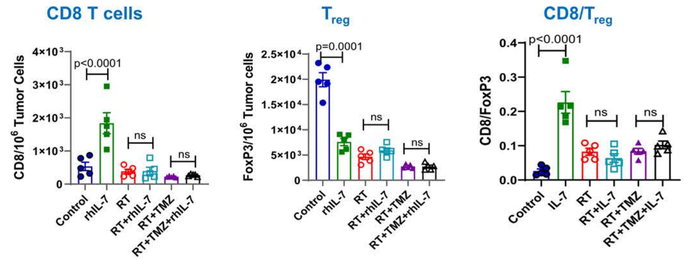

Figure 4. Orthotropic mice bearing GL261 tumors treated with NT-I7 had increased number of CD8 + T cells (*left panel*) and significantly decreased the number of regulatory FoxP3+ T cells (T_{reg}, *middle panel*) within the tumor, resulting in a significantly higher cytotoxic CD8 T cells to T_{reg} ratio within the tumor microenvironment (*right panel*)

CONCLUSIONS

- In the orthotopic GBM mouse model, long acting IL-7 (NT-I7) enhanced cytotoxic CD8+ T cells systemically in lymphoid organs, and improved survival.
- NT-I7 treatment increased the CD8+ T cells but decreased T_{reg} cells within the tumor microenvironment.
- A phase I/II trial to evaluate NT-I7 in patients with high-grade gliomas is presently ongoing (NCT03687957).