Preclinical glioma immunotherapy using advanced rat tumor models

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About ten years ago, the field of experimental glioma immunotherapy emerged from relative obscurity and has expanded rapidly since then. Concurrently, major advances in general immunology fueled progress in the understanding of tumor immunology. Although these advances have not yet benefited many patients, there are clear indications that immunotherapy will become an important aspect of some future clinical anti-glioma treatments. It is a major challenge of our generation to find immunotherapy's optimal context and use for cancer. How might a small group contribute to that development?

Our approach has been to use reproducibly initiated, pathologically advanced animal gliomas to develop and test immunotherapy regimens which could be translated to clinical neuro-oncology. Our initial studies were with the 9L gliosarcoma (9LGS) -- a moderately aggressive malignant brain tumor of the rat. This tumor model is fairly sensitive to radiation, is only modestly invasive and is highly immunogenic. Nevertheless, 10^4 9LGS cells implanted in the rat brain results in the death of 100% of untreated rats 21 ± 3 days later. We initiated therapy on day 14, when the advanced tumors occupy ~2% of the rat brain, roughly the fraction of the human brain occupied by glioblastoma multiforme (GBM) when the latter first presents clinical signs and/or symptoms. We have shown that boron neutron-capture therapy (BNCT), photon radiosurgery (LINAC), and microbeam radiation therapy (MRT) synergize with immunotherapy to significantly increase long-term survival of rats with such advanced 9LGS tumors (1-3). Multiple injections of preirradiated, non-clonogenic 9LGS cells as antigens (I) following BNCT (immunoprophylaxis; IMPR) rescued half of the rats that would have died had they received BNCT alone. LINAC and MRT share the attribute of not acting synergistically with IMPR. However, such synergy can be achieved by multiple injections of preirradiated, non-clonogenic GMCSF-transfected 9LGS cells (gene-mediated immunoprophylaxis; GMI) for both LINAC radiosurgery and MRT. All our experimental data to date support this postulate: The less effective is the radiation therapy, the more aggressive must be the immunotherapy for isoeffective palliation of an advanced malignancy. Our data, therefore, justify much urgency in efforts to improve the efficacies of palliative radiotherapy and radiosurgery for diminishing tumor bulk, ablating tumor vascularity, and reducing the number of viable tumor stem cells.

Using the aggressive, weakly immunogenic F98 rat brain glioma model and a subcutaneous (sc) F98 tumor challenge assay, we showed that GMI had only a modest impact on the progressive growth of sc F98 tumors. However the ablation of T-regulatory cells using a Mab to CD25 followed by GMI (GMI*) was effective at preventing the progressive growth of sc F98 tumors. Accordingly, post-irradiation GMI* was tested in an F98 advanced brain tumor therapy model. Implantation of 10^4 F98 cells into the rat brain reproducibly resulted in deaths of all untreated animals 25 ± 3 days later. Although GMI* following LINAC radiosurgery of such rats did not increase their median day of death, the lives of about 1/3 of them were significantly prolonged. Most importantly, the addition of endogenous adjuvant monosodium urate (MSU) crystals with GMI* (GMI*+MSU)

increased their median post-implantation day of death from 42 to 56, an ≈50% longer survival than that achieved by LINAC radiosurgery (4).

These results will be discussed in the context of some of the current developments in the field of glioma immunotherapy.

References

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