Synergizing hyperthermia and immunotherapy for intracranial tumors

Authors: Aden P. Haskell-Mendoza, Lucas P. Wachsmuth, Richard Tyc, Peter E. Fecci

Funding: Eugene A Stead Jr. Scholarship

Background: Laser interstitial thermal therapy (LITT) is an emerging modality for hyperthermic ablation of brain tumors. Hyperthermia-induced tumor coagulative necrosis may serve as a source of neoantigen for T-cell priming and a subsequent anti-tumor immune response. Methods: Building on our previous experience with subcutaneous hyperthermia, we engineered a model of intracranial LITT. We performed magnetic resonance imaging (MRI)-based segmentations of our aggressive CT-2A glioma model to identify the timepoint at which solid tumor was visible, selecting a site 2 mm posterior to the tumor implantation site for thermal monitoring. Results: Using multiple laser power settings and ablation lengths, we identified a thermal dose of 1 W for 90 s, delivered to non-tumor bearing mouse brains via an implanted 400 μm laser fiber, did not induce mortality at 24 hours. Mice bearing CT-2A tumors subsequently ablated at 10 days following implantation. Ablation was associated with a modest, non-significant benefit in survival, median overall survival relative to sham surgery (mOS) = 22 vs 23 days, P = 0.075. Treatment with dexamethasone 4 μg IP for 7 days beginning on the morning of LITT appeared to make this benefit more apparent, sham vs LITT mOS = 20 vs 22.5 days, P = 0.051. LITT induced peritumoral T2 hyperintensity on serial post-treatment MRI, and produced findings associated with coagulative necrosis on H&E sections of tumor bearing mouse brains. We subsequently performed immune profiling on tumor, peripheral blood, and multiple lymphoid organs to identify a LITT-induced immune signature. Cotreatment with LITT and anti 4-1BB agonist antibodies durably increases survival, 21 vs 26 days, P = 0.0006. Conclusions: Hyperthermia may enhance the efficacy of immunotherapy against intracranial tumors.