Clinical Trial Completed

580 MAPPING INTERSTITIAL FLUID FLOW IN THE BRAIN TO IMPROVE CAR T CELL TRAFFICKING AND EFFICACY

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Background A major obstacle to successful CAR T cell therapy for glioblastoma (GBM) is effective tumor trafficking and infiltration, which is limited by the blood-brain and blood-CSF barriers. Further, the GBM tumor microenvironment (TME) is characterized by solid stress, vessel leakiness, hypoxia, low pH, and high interstitial fluid pressure, all which impact CAR T cell trafficking. In this study, we set out to address two clinical challenges related to CAR T cell trafficking and efficacy: 1) the detection of CAR T cell tumor infiltration and bioactivity using clinical translatable imaging techniques, such as advanced MRI; and 2) the optimization of the route of administration of CAR T-cells for improved trafficking and therapeutic effect.

Methods We are evaluating CAR T-cells as a novel cell-based immunotherapy for treating glioblastoma (GBM) in early phase clinical trials. CAR T-cell therapy has been shown to induce complete regression in at least one case (Brown *et al*. 2016). These results have led to the initiation of a first-in-human phase I CAR T-cell trial for recurrent high-grade glioma patients at City of Hope (NCT02208362). In this study, perfusion imaging was performed on a subset of patients who received MRI pre-treatment and post-resection, and follow-up MRI after 3 treatment cycles roughly one month after initial imaging (n = 41).

Results A decrease in MR-observed tumor volume was significantly correlated to a decrease in contrast leakage into the surrounding tissue (r = 0.369, p = 0.0177*). These results suggest preliminary evidence of vascular normalization in patients who had strong initial response to CAR-T therapy. Immunohistochemistry analysis of patient tumor tissue indicates that endogenous human T cells were distributed around CD31 stained blood vessels (surgical sample analysis of CAR T patients). To better understand how perfusion imaging relates to CAR T cell therapy, we used two syngeneic models of glioma, K-luc and GL261, and characterized fluid flow dynamics during tumor response versus progression, comparing both invasive (K-luc) versus bulky (GL261) tumor growth phenotypes. We also characterized endogenous immune cell subset distribution at the tumor edge and tumor center, such as T cells (CD3, CD4 and CD8), macrophages (CD68 and CD163) and tumor biomarkers-VEGFA, VEGFC, CD31, HIF1a by immunohistochemistry, which were changing with perfusion-diffusion kinetics of the tumor.

Conclusions Ongoing studies are focused on further investigating interstitial fluid flow as an imaging biomarker predictive of response both clinically and pre-clinically.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0580