Combination Local Oncolytic Adenoimmunotherapy and Systemic CAR T-cell Therapies for Advanced Solid Tumor Treatment

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In solid tumors, chimeric antigen receptor-modified T cells (CAR T-cells) must overcome the challenges of the immunosuppressive tumor microenvironment. We hypothesized that pre-treating tumors with our binary oncolytic adenovirus (CAd) that produces local oncolysis and expresses immunostimulatory molecules would enhance the antitumor activity of HER2-specific CAR T-cells, which alone are insufficient to cure solid tumors. We tested multiple cytokines in conjunction with PD-L1 blocking antibody and found that Ad-derived IL-12p70 prevents the loss of HER2.CAR expressing and encoding T-cells at the tumor site (CAd*12_PDL1*). In head and neck squamous cell carcinoma (HNSCC) xenograft models, combining local treatment with CAd*12_PDL1* and systemic HER2.CAR T-cell infusion improved survival to >100 days compared to approximately 25 days with either approach alone. This combination also controlled both primary and metastasized tumors in an orthotopic model of HNSCC. Overall, our data show that CAd*12_PDL1* augments the anti-tumor effects of HER2.CAR T-cells, thus controlling the growth of both primary and metastasized tumors. These results suggest that local treatment of our “all-in-one” vector (oncolysis, checkpoint inhibition, cytokine) can systemically enhance adoptive T cell responses to cancer cells. Based on these preclinical results, we now propose this combinatorial immunotherapy for phase I clinical testing at Baylor College of Medicine.