Section 1

Technical Abstract

POINTS TO CONSIDER

TECHNICAL ABSTRACT

Objectives: To evaluate the safety and persistence of escalating doses of autologous CMV-specific cytotoxic T-lymphocytes (CTL) genetically modified to express chimeric antigen receptors (CAR) targeting HER2 in patients with HER2-positive Glioblastoma multiforme (GBM).

Rationale:
Glioblastoma multiforme (GBM) is the most common primary brain malignancy of adults. The outcome for patients has not improved significantly over the last 2 decades and most patients die of their disease within 2 years of diagnosis. HER2, an established immunotherapeutic target antigen, is expressed in 80% of GBMs at levels that are too low for HER2 monoclonal antibodies such as trastuzumab to be effective. Genetic modification of T cells with chimeric antigen receptors (CARs) is an attractive approach to overcome this limitation, since the overall avidity of receptors arrayed on a T-cell will be greater than the avidity of a bivalent antibody, and engagement of a limited number of T-cell receptor molecules may be sufficient to trigger a cytotoxic effector response. CARs can be made by combining the antigen binding domains of the variable regions of a monoclonal antibody (scFv), a transmembrane domain and signaling endodomains derived from CD28 and the T-cell receptor ζchain. When expressed by T cells, CARs bind the antigen expressed on the target cell surface and activates the lytic pathway of the T cells. We have cloned a CAR targeting the tumor associated antigen HER2 into the retroviral vector SFG. T cells expressing this HER2-specific CAR killed HER2-positive GBM cells ex vivo and in animal models.

Incorporation of a single co-stimulatory endodomain in the CAR cannot readily compensate for the complex temporo-spatial interactions of the multiplicity of costimulatory molecules and ligands involved in the physiological activation of effector T-cell subsets. In previous studies in neuroblastoma we have overcome this deficit by expressing tumor directed CARs in EBV-specific CTLs. In this clinical study we propose to express HER2 CARs in CMV-specific CTLs since GBMs are positive for CMV antigens. Thus HER2 CAR/CMV-specific CTLs (CAR-CTLs) will recognize the tumor through both the chimeric and their native receptor. In addition, CAR-CTLs will receive co-stimulation when their native receptor is engaged by CMV antigens presented on professional antigen presenting cells.

Study design:
This is a Phase I dose escalating clinical trial to evaluate the safety of CMV-specific CTL expressing a HER2 CAR in patients with recurrent/progressive GBM. One SFG vectors will be used to generate autologous CAR-CTLs and three dose levels will be evaluated namely, 1.5×10^7 cells/m^2 (dose level 1), 4.5×10^7 cells/m^2 (dose level 2) and 1.2×10^8 cells/m^2 (dose level 3). We will assess the safety of the infused T cells and measure their survival and antitumor effects.