

ABSTRACT

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Locoregional infusion of HER2-specific CAR T cells in children and young adults with recurrent or refractory CNS tumors: an interim analysis.

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Locoregional delivery of chimeric antigen receptor (CAR) T cells has resulted in objective responses in adults with glioblastoma, but the feasibility and tolerability of this approach is yet to be evaluated for pediatric central nervous system (CNS) tumors. Here we show that engineering of a medium-length CAR spacer enhances the therapeutic efficacy of human erb-b2 receptor tyrosine kinase 2 (HER2)-specific CAR T cells in an orthotopic xenograft medulloblastoma model. We translated these findings into BrainChild-01 (NCT03500991), an ongoing phase 1 clinical trial at Seattle Children's evaluating repetitive locoregional dosing of these HER2-specific CAR T cells to children and young adults with recurrent/refractory CNS tumors, including diffuse midline glioma. Primary objectives are assessing feasibility, safety and tolerability; secondary objectives include assessing CAR T cell distribution and disease response. In the outpatient setting, patients receive infusions via CNS catheter into either the tumor cavity or the ventricular system. The initial three patients experienced no dose-limiting toxicity and exhibited clinical, as well as

correlative laboratory, evidence of local CNS immune activation, including high concentrations of CXCL10 and CCL2 in the cerebrospinal fluid. This interim report supports the feasibility of generating HER2-specific CAR T cells for repeated dosing regimens and suggests that their repeated intra-CNS delivery might be well tolerated and activate a localized immune response in pediatric and young adult patients.

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