GD2-CAR T cell therapy

Mount et al. used anti-GD2 chimeric antigen receptor (CAR)-modified T cells to target GD2 [1].

Majzner et al. previously discovered that the disialoganglioside GD2 is highly expressed on H3K27M-mutant glioma cells and demonstrated promising preclinical efficacy of GD2-directed chimeric antigen receptor (CAR) T cells, providing the rationale for a first-in-human Phase 1 clinical trial (NCT04196413). Because CAR T-cell-induced brainstem inflammation can result in obstructive hydrocephalus, increased intracranial pressure, and dangerous tissue shifts, neurocritical care precautions were incorporated. Here we present the clinical experience from the first four patients with H3K27M-mutant DIPG/DMG treated with GD2-CAR T cells (GD2-CART) at dose level 1 (1e6 GD2-CAR T cells/kg administered intravenously). Patients who exhibited clinical benefit were eligible for subsequent GD2-CAR T infusions administered intracerebroventricularly3. Toxicity was largely related to tumor location and reversible with intensive supportive care. On-target, off-tumor toxicity was not observed. Three of four patients exhibited clinical and radiographic improvement. Proinflammatory cytokines were increased in plasma and cerebrospinal fluid (CSF). Transcriptomic analyses of 65,598 single cells from CAR T cell products and CSF elucidate heterogeneity in response between subjects and administration routes. These early results underscore the promise of this approach for H3K27M+ DIPG/DMG therapy [2].

Although GD2-CAR T-cells demonstrated significant anti-tumor activity against Diffuse midline glioma H3 K27M-mutant in vivo, a multimodal approach may be needed to more effectively treat patients. de Billy et al. investigated GD2 expression in DMG/DIPG and other pediatric high-grade gliomas (pHGG) and sought to identify chemical compounds that would enhance GD2-CAR T-cell anti-tumor efficacy.

Immunohistochemistry in tumor tissue samples and immunofluorescence in primary patient-derived cell lines were performed to study GD2 expression. We developed a high-throughput cell-based assay to screen 42 kinase inhibitors in combination with GD2-CAR T-cells. Cell viability, western blots, flow-cytometry, real time PCR experiments, DIPG 3D culture models and orthotopic xenograft model were applied to investigate the effect of selected compounds on DIPG cell death and CAR T-cell function.

GD2 was heterogeneously, but widely, expressed in the tissue tested, while its expression was homogeneous and restricted to DMG/DIPG H3K27M-mutant cell lines. We identified dual Insulin-like growth factor 1 receptor(IGF1R/IR) antagonists, BMS-754807 and linsitinib, able to inhibit tumor cell viability at concentrations that do not affect CAR T-cells. Linsitinib, but not BMS-754807, decreases activation/exhaustion of GD2-CAR T-cells and increases their central memory profile. The enhanced anti-tumor activity of linsitinib/GD2-CAR T-cell combination was confirmed in DIPG models in vitro, ex vivo and in vivo.

The study supports the development of IGF1R/IR inhibitors to be used in combination with GD2-CAR T-cells for Diffuse midline glioma H3 K27-altered treatment and, potentially, by pHGG [3].

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Mount CW, Majzner RG, Sundaresh S, et al. Potent antitumor efficacy of anti-GD2 CAR T cells in H3-K27M+ diffuse midline gliomas. Nat Med. 2018;24(5):572-579.
2)

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3)

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