PDGFRα-SPECIFIC CAR T CELL THERAPY OF PEDIATRIC HIGH-GRADE GLIOMA

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Background Platelet-derived growth factor receptor alpha (PDGFRα) is a tyrosine kinase receptor that plays a pivotal role in tumorigenesis and is associated with tumor proliferation and progression. Pediatric gliomas are known to express high levels of PDGFRα, designating the receptor a viable target for chimeric antigen receptor (CAR) T cell therapy.

Methods Lentiviral vectors encoding PDGFRα-specific CAR-encoding sequences were constructed by fusion of a single chain Fv (scFv) to a human CD8a stalk and transmembrane domain linked to either a CD28 or CD137 intracellular signaling domain fused with a terminal CD3ζ domain. PDGFRα-specific CAR T cells were expanded with IL-2 and artificial antigen presenting K562 cells (aAPC) expressing truncated PDGFRα. The cytotoxic function of PDGFRα-CAR T cells was assessed using in vitro killing assays. The therapeutic efficacy was evaluated in a mouse KNS42 glioma model. KNS42 cells expressing firefly luciferase and green fluorescent protein (ffLuc-GFP) were engrafted into the right parietal lobe of NSG mice using screw-guided injections. Intratumoral treatment with PDGFRα-CAR T cells was carried out one week later, and tumor growth was monitored weekly over the course of nine weeks by bioluminescence imaging.

Results All CAR T cells demonstrated over 75% CAR expression two weeks following transduction and expansion. In vitro cytotoxicity assays demonstrated PDGFRα-specific lysis of KNS42 and PDGFRα-U87 glioma cells. PDGFRα-CAR T cells expressing the CD28 signaling domain exhibited a higher level of cytotoxicity against target KNS42 cells. Both PDGFRα-CD28 and -CD137 CAR T cell products resulted in decreased tumor progression when compared to the control mice injected with saline (figure 1). However, PDGFRα-CD28-CAR T cells exhibited a higher level of antitumor activity than PDGFRα-CD137 CAR T cells (97% vs 85% inhibition), consistent with the in vitro cytotoxicity observations (figure 1).

Conclusions In this study, we evaluated and compared the efficacy of PDGFRα-CAR T cells expressing the CD28 or CD137 costimulatory domains in controlling the growth of pediatric glioma cells. We have demonstrated that PDGFRα-CD28 CAR T cells exhibited more immediate anti-tumor response resulting in a more significant long-term reduction of tumor progression. Repeated administration of PDGFRα-CD28 CAR T cells may be warranted in future studies to further improve outcomes and preserve long-term responses. Our preclinical studies demonstrate the therapeutic potential for PDGFRα-CAR T cell in the treatment of pediatric high-grade glioma and set the stage for future clinical translation.

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Ethics Approval All animal studies were conducted at MD Anderson with approval and in accordance with Institutional Animal Care and Use Committee (IACUC) guidelines. Mice were housed in pathogen-free conditions and were monitored daily for welfare and any signs of discomfort or pain. All efforts were made to minimize animal suffering, and moribund mice were humanely euthanized according to IACUC guidelines. The ID number of approval for the animal study is 00001237-RN02.