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Prospects for Chimeric Antigen Receptor T-Cell Therapy in the Treatment of Glioblastoma Multiforme: A Review of the Literature

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Genetically modified autologous T-cells for the expression of chimeric antigen receptors (CARs) have brought attention to the dawn of a novel era of cancer immunotherapy due to the potential shown by the yield of monumental clinical outcomes in past studies. Impressive clinical responses found with CAR T-cell therapy for hematologic malignancies have led to the investigation of CAR T-cells in solid tumors, although the attainment of similar results with such malignancies has been challenging to date. Despite some progress over the past decade, Glioblastoma Multiforme (GBM) continues to present as a particularly challenging malignancy for treatment and the prognosis remains poor for a vast majority of patients. However, recent data shows supporting evidence of the safety and clinical efficacy of CAR T-cell therapy use in treating GBM. This review will discuss the challenges commonly associated with treating GBM and new strategies by which CAR T-cells can overcome such barriers. In addition, emergence of recently conceived techniques for optimizing CAR T-cell therapy in GBM will be addressed to highlight the prospective promise of this novel immunotherapy. Chimeric antigen receptors (CARs) are recombinant protein molecules redirected to target specific cells and have shown high therapeutic responses in the treatment of hematologic malignancies. Glioblastoma multiforme (GBM) is an extremely difficult-to-treat solid tumor with limited current therapies various aspects have made CAR T-cells appealing for GBM, including the ability to surpass the blood-brain-barrier and function human leukocyte antigen (HLA) independently. Recent innovative solutions have begun to optimize CAR T-cells for use in GBM. Recent animal models and human trials have shown clinical efficacy in utilizing CAR T-cells to treat glioblastoma multiforme. IL-13Rα2, a protein that regulates immune responses by binding cytokine IL-13, has been shown to be over expressed in 44% of GBM tumor samples as suggested by oligonucleotide microarray data sets. Because IL-13Rα2 is not significantly expressed on normal brain tissue and is expressed on glioma stem-like cells, recent trials have proven IL-13Rα2 as a plausible antigen target for CAR T-cell therapy in GBM. Though development of CAR T-cells was lengthy (3-4 months), the trial indicated the feasibility and efficacy in constructing IL-13Rα2-directed CD8+ cytotoxic T lymphocytes for recurrent GBM with construction success in 10 out of 13 patients. Though implementing CAR T-cell therapy for solid tumors has seen slowed development, recent clinical trials have highlighted the prospective promise for the therapy in the uniformly fatal tumor, glioblastoma multiforme. Given T-cells can penetrate the blood-brain-barrier and function HLA-independently; numerous aspects have attracted the use of CAR T-cells for GBM. Nevertheless, the path ahead poses various challenges for optimal CAR T-cell use in GBM, including the immunosuppressive GBM microenvironment, rampant tumor heterogeneity, and inability to traffic T-cells to antigen sites. However, with the development of innovative solutions, including cytokine co-expressed CAR T-cells, tandem CAR T-cells, and intracranial administration, numerous CAR constructs have proven to be more effective in treating GBM. Though, the Food and Drug Administration has not hitherto approved a CAR T-cell therapy for solid tumors, an expanding number of clinical trials continue to highlight possible areas of improvement and the promising prospects of the therapy's use in GBM.