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Clinical progress in the development of CAR T cells to treat malignant glioma

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Abstract

Context: Chimeric antigen receptor (CAR) T cell therapy is an exciting modality of immunotherapy that has revolutionized the treatment of hematologic malignancies. However, translating this success to malignant gliomas such as glioblastoma (GBM) and diffuse midline glioma (DMG) remains a formidable challenge due to multiple biologic, anatomic, and immunologic factors. Despite these hurdles, a number of clinical trials deployed over the last decade have increased optimism for the potential of CAR T cell therapy in glioma treatment.

Evidence synthesis: We highlight historical and ongoing clinical trials of CAR T cell therapy in glioma, with a focus on key tumor-associated antigens such as IL-13Rα2, HER2, EGFR, EGFRvIII, EphA2, GD2, and B7-H3. Early studies established proof-of-concept for antigen-specific CAR T cell targeting, yet immune evasion mechanisms such as antigen downregulation and limited CAR T cell persistence remain significant obstacles. Recent approaches, including multiantigen targeting, alternative cell sources, and innovations in delivery routes offer promising strategies to overcome these challenges.

Conclusions: The rapid evolution of investigational CAR T cell therapies portends great potential for the future of glioma treatment. Future studies will need to refine antigen targeting strategies, optimize CAR T cell persistence, and integrate combinatorial approaches to fully harness the therapeutic potential of this modality and improve the therapeutic window against brain tumors.

Keywords: CAR T cell therapy; Cell engineering; Glioma; Phase I clinical trials; Tumor antigens; Tumor immune evasion.