Molecular Therapy
Commentary

Three recent breakthroughs in CAR T cells for the treatment of glioblastoma: Is it the light at the end of the tunnel?

Pedro R. Lowenstein,[1,2,3] Maria Luisa Varela,[1] and Maria G. Castro[1,2]

https://doi.org/10.1016/j.ymthe.2024.04.018

Glioblastomas always become resistant to standard-of-care (SOC) therapies: surgery, radiotherapy, and chemotherapy (with the eventual addition of tumor-treating fields). Strictly validated results exist for these three SOC therapies. However, doubts have been raised recently, as some trials used suboptimal controls, while other crucial trials were performed before the discovery of isocitrate dehydrogenase 1 (IDH1)-mutated tumors, which makes tumors less aggressive. Given that patients with tumors harboring the IDH1-R132H mutation have significantly better survival, an unbalanced inclusion of these patients in clinical trials could have biased the data, resulting in longer survival being erroneously attributed to response to therapies. Indeed, a post hoc analysis of the CATNON trial (ClinicalTrials.gov: NCT00626990) showed that the addition of temozolomide did not enhance survival beyond that provided by radiotherapy in patients whose tumors were IDH1 wild type, indicating the need for new large randomized clinical trials selectively targeting patients with tumors expressing either wild-type or mutated IDH1.[1] The lack of established therapies for tumor recurrence further darkens patients' outlooks. Although immune checkpoint inhibitors have made significant inroads in the treatment of melanomas and several other tumors, these drugs have shown no consistent therapeutic benefit in glioblastoma. Whether it is the suppressive tumor immune microenvironment teeming with inhibitory myeloid-derived suppressor cells, the presence of the powerful immune suppressor dexamethasone given to patients to inhibit potentially deadly brain edemas,[2] or the lack of a robust influx of armed and activated effector T cells, immunotherapies have yet to demonstrate their utility in the fight against glioblastoma. Despite the current challenges in immunotherapy for glioblastoma, three papers published in *Nature Medicine* and the *New England Journal of Medicine* in the first 2 weeks of March 2024 have moved the needle forward toward making chimeric antigen receptor T cells (CAR T cells) a new treatment modality for glioblastoma.[3–5]

Instead of relying upon the classical pathway of T cell activation, the T cell receptor (TCR) in engineered CAR T cells is replaced by an antibody molecule that will stimulate T cell activation upon binding to the selected target antigens. To bypass the restrictions imposed by the natural TCR, investigators use a chimeric molecule with high affinity for pre-determined antigens expressed by the target cancer cells and link it to transduction elements for the CAR to signal T cell activation and killing. The original idea, constructs named T-bodies, was first implemented in 1989 by Zelig Eshhar and collaborators from The Weizmann Institute in Israel.[6] However, limitations in transducing T cells to express the transgenic T-bodies, later identified as CARs, posed a significant challenge. Thankfully, this challenge was surmounted in 1996 by the development of engineered viral vectors, especially lentiviral vectors, by Naldini, Verma, and Trono at The Salk Institute. This innovation made it possible to insert CARs into T cells to completely redirect T cells to predetermined antigens expressed by the target cancer cells.[7] Twenty years later, groups led by Carl June (University of Philadelphia)[8] and Michel Sadelain (Memorial Sloan Kettering Cancer Center)[9] constructed CAR T cells that were powerful enough to recognize, attack, and destroy various leukemias in children and adults. Once the side effects were tamed, the results were nothing short of fantastic. CAR T cells are now approved by the US Food and Drug Administration and are part of the armamentarium for the treatment of childhood and adult leukemias. The success of CAR T cells in the treatment of liquid cancers led researchers to determine whether this treatment modality could be successful in glioblastoma.

Following their breakthrough publications in 2015 and 2016, Brown et al. have presented data from a phase 1 clinical trial including 65 patients suffering from recurrent glioblastoma who were treated with CAR T cells redirected to recognize interleukin-13 receptor α2 (IL-13Rα2).[3] Patients received 3–4 injections of CAR T cells directly into the tumor or lateral ventricle or in both locations (Figure 1). The maximum amount of CAR T cells delivered per infusion cycle was 2×10^8, and dose-limiting toxicity (DLT) was not reached. In 29 out of 58 patients, stable disease was attained, with two partial responses and two complete responses. The median survival for patients with recurrent glioblastoma was 7.7 months. By contrast, the median survival for patients who received the highest doses in both the tumor and lateral ventricle was 10.2 months.

Bagley et al. have also recently published interim results from a phase 1 trial including 6 patients with multifocal recurrent glioblastoma who received intrathecal injections of bivalent CAR T cells targeting both IL-12Rα2 and EGFR (Figure 1).[4] Two doses of CAR T cells, 1×10^7 and 2.5×10^7, were injected, and the authors reported responses in 3 patients treated with either dose. The

[1]Department of Neurosurgery, The University of Michigan, Ann Arbor, MI 48109, USA; [2]Department of Cell and Developmental Biology, The University of Michigan, Ann Arbor, MI 48109, USA; [3]Department of Biomedical Engineering, The University of Michigan, Ann Arbor, MI 48109, USA

Correspondence: Pedro R. Lowenstein, Department of Neurosurgery, The University of Michigan, Ann Arbor, MI 48109, USA.
E-mail: pedrol@umich.edu