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EDITORIAL

Advances in the Optimization of CAR-T-Cell-Based Therapeutic Approaches to Enhance Antitumor Efficacy in Glioblastoma Treatment

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ABSTRACT

Chimeric antigen receptor (CAR)-T cell therapy is emerging as a promising immunotherapeutic modality for improving clinical outcomes in high-grade gliomas. Three recent studies have demonstrated the safety and feasibility of intracranial CAR-T cell administration in patients with glioblastoma (GBM), along with preliminary evidence of rapid but transient objective responses. These findings provide a rationale for further clinical investigation of this approach.

Keywords: CAR-T cells; Glioblastoma; High-grade gliomas; CARv3-TEAM-E; Bivalent CAR-T

EDITORIAL

Glioblastoma (GBM) is the most aggressive primary tumor of the central nervous system, characterized by poor prognosis and limited treatment options, with a 5-year patient survival rate of less than 10% [1].

The conventional therapeutic protocol that involves the use of surgery followed by radiotherapy and chemotherapy has a high recurrence rate, and there is an unmet need for the identification of novel effective treatment options [2].

Although chimeric antigen receptor (CAR)-T cells represent a promising approach to hematologic malignancies, the application of CAR-T cells in solid tumors still represents a difficult slope to climb, primarily owing to the difficulty of selectively targeting a single antigen in biologically heterogeneous malignancies, as well as the presence of immunosuppressive pathways within the tumor microenvironment.

After years of substantial failures of immunotherapy in the treatment of GBM, recent early studies have shown how the use of CAR-T cells could change the course of GBM, leading to rapid antitumor CAR-mediated responses, albeit often of short duration.

Three recent publications have provided valuable insights into the therapeutic potential of CAR-T cell approaches in the context of GBM management.

Preliminary data from these studies suggest that the implementation of advanced strategies, including bivalent and dual-targeting CAR-T cell therapies, as well as CAR-T cells engineered to

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secrete therapeutic antibodies, aims to overcome the challenges in treating GBM, including the immunosuppressive nature of the tumor microenvironment and the frequent downregulation of tumor-associated surface antigens, collectively hindering effective immunotherapeutic responses.

Brown et al. [3] presented the results from a phase I clinical trial evaluating the locoregional administration of CAR-T cells engineered to target interleukin (IL)-13Rα2, a well-characterized antigen, in a cohort of 65 patients with recurrent high-grade glioma. The study explored three distinct modalities of T cell delivery, viz. intratumoral, intraventricular, and combined administration, and patients received three doses (weekly infusions) of CAR-T cells. The therapeutic regimen demonstrated a favorable safety profile, with no dose-limiting toxicities or treatment-related adverse events exceeding grade 3 severity. Among the 58 patients evaluable for therapeutic response, 50% demonstrated disease control, achieving stable disease or an objective response. Nevertheless, for recurrent GBM, median overall survival for all patients was 7.7 months, an outcome that appears suboptimal when compared with previous studies conducted in the same treatment setting [4].

Choi et al. [5] published the findings from a prespecified interim analysis of the first-in-human, nonrandomized, open label, phase I INCIPIENT study (ClinicalTrials.gov no. NCT05660369). They disclosed the results of the administration of CARv3-TEAM-E through an Ommaya reservoir on the first three patients included in the trial, all diagnosed with recurrent GBM. CARv3-TEAM-E is a second-generation CAR-T cell construct targeting the EGFRvIII antigen, a mutated form of the epidermal growth factor receptor (EGFR) expressed on the surface of GBM cells but absent from healthy tissues. In parallel with targeting EGFRvIII-expressing cells, this CAR-T cell is engineered to induce the secretion of antibodies (TEAM-E) that bind both T cells and the wild-type EGFR. This dual mechanism redirects the immune response against the entire tumor cell population, including both EGFRvIII-positive cells and those lacking the mutation. Treatment with CARv3-TEAM-E T cells resulted in an impressive treatment response, characterized by tumor shrinkage of > 30% occurring within days after receipt of a single intraventricular infusion, without adverse events greater than grade 3. Nonetheless, despite the remarkable rapid antitumor response among the first three patients, the authors observed GBM recurrence after a single infusion of CAR-T in two out of the three cases examined, while the third maintained a durable response for 6 months. The patient who exhibited a sustained clinical response was a 72-year-old male who demonstrated a 18% reduction in tumor volume within 48 h post-treatment initiation. By 2 months post-infusion, the tumor had further regressed by up to 60% relative to baseline measurements. This notably robust and unanticipated response was maintained for up to 6 months following completion of therapy. From a safety standpoint, no dose-limiting toxicities were reported across the patient cohort. All three individuals developed febrile episodes, effectively managed with anakinra; one participant experienced grade 3 encephalopathy lasting 3 days, and two participants developed transient pulmonary ground-glass opacities, which were asymptomatic and resolved spontaneously within 4–6 weeks.

Bagley et al. [6] investigated the administration of intrathecally delivered bivalent CAR-T cells co-targeting EGFR and IL13Rα2 in a cohort of six patients with recurrent GBM. Local administration of the CAR-T cells proved to be both feasible and well tolerated, and in all six patients, the initial follow-up magnetic resonance imaging (MRI), performed within 24–48 h following intraventricular CAR-T cell administration, revealed measurable tumor volume reduction, consistent with partial regression. In several cases, this response was sustained over an extended period, persisting well beyond 28 days. Although none of the patients met the formal Response Assessment in Neuro-Oncology (RANO) criteria for objective response (defined as ≥ 50% reduction in lesion size sustained for at least 4 weeks), three individuals exhibited a ≥ 30% decrease in tumor burden, and among the four patients with at least 2 months of follow-up, three maintained stable disease. Treatment-related adverse events were observed, primarily including headache, nausea, vomiting,

and tumor inflammation–associated neurotoxicity (TIAN), occasionally accompanied by mild cytokine release syndrome (CRS). These events were predominantly low grade and manageable, with no reported grade 4 or 5 toxicities.

It is important to reiterate that the data in both cases derive from interim analyses, which will need to be reevaluated in a broader context upon completion of the studies. Moreover, these are phase I trials primarily focused on safety assessment and the determination of the maximum tolerated dose. Nevertheless, these preliminary analyses provide a basis for several important considerations: First, CAR-T cell therapy in the setting of GBM recurrence appears to be feasible and to have a favorable safety profile. Secondly, intracranial delivery should be considered the optimal administration route, given it is the only delivery mechanism associated with meaningful radiographic responses to CAR-T cell therapy. Thirdly, a critical point, novel strategies such as bivalent or dual-antigen targeting CAR-T cell constructs, as well as CAR-T cells engineered to secrete therapeutic antibodies (such as CAR-T cells co-targeting EGFR and IL13Rα2 and CARv3-TEAM-E) have emerged as promising approaches to overcome the challenge posed by GBM heterogeneity, capable of eliciting objective radiographic responses. Undoubtedly, a critical point in these studies is likely to be the targets. Among the recurrent genetic aberrations identified in GBM, the EGFR amplification and the EGFRvIII mutation are prevalent; nonetheless, their prognostic significance continues to be disputed in the literature [7, 8], and antibodies targeting EGFRvIII have not demonstrated a meaningful impact on survival [9]. IL-13 receptor subunits α1 and α2 are overexpressed in GBM and are associated with a significantly lower survival rate irrespective of tumor treatment [10, 11]. Given the absence of a universally expressed and targetable antigen in GBM, ongoing efforts should focus on multitargeted CAR-T platforms or CAR-T cells armed with cytotoxic or immune-stimulatory payloads to enhance antitumor efficacy. Another pivotal consideration is that, although a prompt antitumor effect from CAR-T cells has been detected, with measurable responses emerging within a few days post-infusion, the response proved to be transient. Indeed, administration of a single CAR-T cell infusion appears inadequate for eliciting durable therapeutic responses, and strategies specifically designed to enhance durability are warranted. The limited durability of clinical benefit, coupled with the therapy's complex manufacturing process and substantial financial burden, raises critical concerns regarding the cost-effectiveness and long-term utility of CAR-T cells in this aggressive and highly heterogeneous malignancy. These therapies involve a multistep process requiring highly specialized facilities, rigorous quality control, and significant time and labor. Additionally, the need for personalized production limits scalability and drives up per-patient costs. The infrastructure required to support CAR-T administration, including lymphodepleting chemotherapy, inpatient monitoring, and management of potentially severe adverse events such as cytokine release syndrome and neurotoxicity, further contributes to the overall expense. Lastly, substantial research and development investments, regulatory hurdles, and limited competition in this emerging therapeutic field also play a significant role in maintaining high manufacturing costs. As a final observation, the most significant evidence on the application of CAR-T is in the setting of GBM recurrence; on the contrary, in newly diagnosed GBM, the use of CAR-T cells in combination with pembrolizumab has proven to be ineffective [12].

CONCLUSIONS

Although CAR-T cell therapies have gained regulatory approval for hematologic malignancies, their application in solid tumors remains significantly limited. In particular, the deployment of CAR-T cells in GBM has faced substantial challenges, chiefly the difficulty of targeting a single tumor-associated antigen in a biologically heterogeneous setting, and the presence of immunosuppressive elements within the tumor microenvironment. Furthermore, CAR-T cell therapies are associated with high costs due

to a combination of factors inherent to their complexity and individualized manufacturing process.

While the rapid tumor regressions observed in these studies offer a degree of optimism, caution remains warranted. These findings do not constitute a definitive cure for GBM; however, the observed tumor volume reductions represent a meaningful step forward following years of limited progress. The initiation of a therapeutic approach capable of eliciting measurable tumor regression offers a promising foundation for future development. Key variables that still require refinement include the optimal timing of CAR-T cell administration, integration with pre-infusion chemotherapy to enhance efficacy, and stratification of patients on the basis of molecular tumor profiling.

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Declarations

Conflict of Interest. Lidia Gatto, Vincenzo Di Nunno, Alicia Tosoni, Marta Aprile, Stefania Bartolini, Chiara Maria Argento, Marzia Margotti, and Enrico Franceschi declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Enrico Franceschi is an Editorial Board member of *Oncology and Therapy*. Enrico Franceschi was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

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