The update of chimeric antigen receptor-T cells therapy in glioblastoma

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Abstract: Glioblastoma (GBM) is the most malignant central nervous system neoplasm and the outcome is difficult to break through for decades. Ninety percent of patients who suffered from treatment failed. Since 2010, the chimeric antigen receptor (CAR)-T cell therapy has achieved a durable effect in the treatment of B-cell hematologic malignancies. Although several preclinical and clinical trials have emerged as a potential option in solid tumor including high-grade gliomas, the results are limited at present. The challenges of CAR-T cells in GBM are including identification of tumor-specific antigens, preservation activity of T cell, trafficking of enough CAR-T cells to the tumor site, and reversed unique immune suppressive environment of the central nervous system. The success of targeting brain tumors with CAR-T cells has more consideration. In this review article, we will summarize the current key clinical trials of CAR-T therapies in this field. And will outline the obstacles of application of CAR-T cells for the treatment of GBM as well. This review is intended to help guide the future direction of CAR-T therapy in GBM that will move the outcome forward in the future.

Keywords: Brain tumors; Chimeric antigen receptor T cells; Glioblastoma; Immunotherapy

1. INTRODUCTION

Glioblastoma (GBM) is the most common and malignant brain tumor. Despite the advance, multimodality of treatment strategy including the extent of surgical resection, concurrent chemotherapy (Temozolomide) and radiotherapy and maintenance chemotherapy, the survival rate has remained difficult to improve until now. The use of bioengineering T cells as an anti-cancer tool has been explored extensively over the past years. In 1989, Gross et al[1] had designed the construction of genetically engineered modified human cytotoxic T cells with the expression of chimeric surface receptors. Therefore, the T cells can be endowed with the specificity for any surface protein expressed by cancer cells. Since 2010, the clinical experience of chimeric antigen receptor (CAR)-T cell therapy for B-cell lymphoma has achieved durable complete remissions after infusions of these bioengineering cellular products. In 2017, CAR-T cells targeting CD19 for B-cell lymphoma were approved by the Food and Drug Administration of the United States and have revolutionized the treatment of hematologic malignancies. However, unlike the success of the use of CAR-T cells have seen in B-cell lineage leukemia and lymphoma, the efficacy in solid tumors including high-grade glioma such as GBM has been shown limited anti-cancer ability. Both T cell and tumor-intrinsic factors contribute to treatment failure of GBM as well as B-cell malignancies.

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2. TUMOR SPECIFIC TARGET OF CAR-T THERAPIES IN GBM

GBM still exhibits poor and dismal disease. Its median life expectancy is approximately 15 months.[2,3] Well-defined targets for GBM are interleukin-13 receptor subunit alpha-2 (IL13Rα2), epidermal growth factor receptor variant III (EGFRvIII), human epidermal growth factor receptor 2 (HER2), ephrin type-A receptor 2 (EphA2), and B7-H3. Clinical trials with response reports/no reports are summarized in Table 1 and Table 2.[3–7] The GBM specific targets were shown in Table 3.[8–14]

2.1. Interleukin-13 receptor subunit alpha-2

A recent report by Brown et al[3,4] presents a case with recurrent GBM underwent repeat resection and followed by intracranial infusion of CAR-T cells targeting antigen IL13Rα2. IL13Rα2 is a GBM associated plasma membrane receptor, which is the high expression in GBM. After the surgical resection, the CAR-T cells were administered by two steps: weekly infusions of CAR-T cells into the tumor resection cavity for 6 weeks, and followed

Table 1

Published clinical studies with CAR-T therapy for GBM

Target antigen	Trial	Aim	N	Outcome
IL13Rα2	NCT00730613 (City of Hope[4])	First trial to evaluate intracranial delivery of IL13Rα2 CAR-T in recurrent GBM	3	Median OS 10.9 mo
	NCT02208362 (City of Hope[3])	To determine safety of intracranial tumor/ventricular delivery in recurrent GBM	Ongoing	One case demonstrated CAR-T mediate complete response for at least 7.5 mo
EGFRvIII	NCT02209376 (University of Pennsylvania[5])	To determine the safety and efficacy of single-dose IV EGFRvIII CAR-T in recurrent GBM	10	Median OS 8.3 mo 1/10 extended SD, alive at 18 mo Decreased EGFRvIII expression (5/7 pts)
	NCT01454596 (National Cancer Institute[6])	To determine safety and efficacy of IV EGFRvIII CAR-T and IL-2 following lymphodepletion in recurrent GBM	18	Median PFS 1.3 mo Median OS 6.9 mo 1/18 PFS of 12.5 mo and alive at 59 mo
HER2	NCT01109095 (Baylor Collage[7])	To determine the safety and efficacy of HER2 CAR-T in adult and pediatric recurrent GBM	16	Median OS 11.1 mo 1/16 PR, 7/16 SD (3 pt SD for 24-29 mo)

CAR-T = chimeric antigen receptor-T cell; EGFRvIII = epidermal growth factor receptor variant III; GBM = glioblastoma; HER2 = human epidermal growth factor receptor 2; IL13Rα2 = interleukin-13 receptor subunit alpha-2; IL-2 = interleukin-2; IV = intravenous; OS = overall survival; PFS = progression-free survival; PR = partial response; SD = stable disease.

Table 2

Unreported CAR-T clinical trials including malignant gliomas

Clinical trial and institution	Target	Phase	N	Study name	Status
NCT02331693 (RenJi Hospital)	EGFR	1	10	CAR-T cells in Treating Patients With Malignant Gliomas Overexpressing EGFR	Completed, unknown
NCT03252171 (Fuda Cancer Hospital)	GD2	1/2	60	CAR-T cell Immunotherapy for GD2 Positive Glioma Patients	Completed
NCT02575261(Fuda Cancer Hospital)	EphA2	1/2	60	CAR-T cell Immunotherapy for EphA2 Positive Malignant Glioma Patients	Completed
NCT02713984 (Southwest Hospital)	HER2	1/2	60	A Clinical Research of CAR T cells Targeting HER2 Positive Cancer	Recruiting
NCT03283631 (Duke University)	EGFRvIII	1	24	Intracerebral EGFR-vIII CAR-T cells for Recurrent GBM (INTERCEPT)	Recruiting
NCT02844062 (Beijing Sanbo Brain Hospital)	EGFRvIII	1	20	Pilot Study of Autologous Anti-EGFRvIII CAR T cells in Recurrent Glioblastoma	Recruiting
NCT03170141 (Shenzhen Geno-immune Medical Institute)	EGFRvIII	1/2	20	4SCAR-IgT Against Glioblastoma	Enrolling by invitation
NCT02442297 (Baylor College)	HER2	1	14	T cells Expressing HER2-specific Chimeric Antigen Receptors (CAR) for Patients With Glioblastoma (iCAR)	Recruiting
NCT02937844 (Beijing Sanbo Brain Hospital)	PD-L1	1	20	Pilot Study of Autologous Chimeric Switch Receptor Modified T cells in Recurrent Glioblastoma	Recruiting

CAR-T = chimeric antigen receptor-T cell; EGFR = epidermal growth factor receptor; EGFRvIII = epidermal growth factor receptor variant III; EphA2 = ephrin type-A receptor 2; GD2 = Disialoganglioside; HER2 = human epidermal growth factor receptor 2; PD-L1 = programmed cell death ligand 1.

Table 3

GBM associated target antigens

Antigen	Expression percentage in GBM	Expression on normal tissue
B7-H3	58%[8]	Liver, heart, lung, kidney, prostate, breast, placenta, bone marrow, lymphoid organ
EGFRvIII	30%[9]	Restricted
EphA2	90%[10]	Epithelial tissue
GD2	80%[11]	CNS, peripheral nerves
HER2	81%[12]	Lung, epithelial tissue, skin, muscle and lymphoid organ
IL13Rα2	58%[13]	Testis, pituitary gland
PD-L1	88%[14]	Lung, heart, airway epithelial tissue, placenta and myeloid cell

CNS = central nervous system; EGFRvIII = epidermal growth factor receptor variant III; EphA2 = ephrin type-A receptor 2; GBM = glioblastoma; GD2 = Disialoganglioside; HER2 = human epidermal growth factor receptor 2; IL13Rα2 = interleukin-13 receptor subunit alpha-2; PD-L1 = programmed cell death ligand 1.

by intrathecal infusion after the new lesions were found. The imaging study showed a dramatic response with shrinkage of all lesions by 77% to 100%.[3] The safety of this approach has been proved previously.[4] However, distant tumor recurrence was found about 7.5 months after the initiation of CAR-T therapy. In this study, the CAR-T cells were infusion through two way including into the resection cavity and cerebrospinal fluid, suggesting that different routes to administer immunotherapies should be considered in brain tumors.[15,16]

2.2. Epidermal growth factor receptor variant III

EGFRvIII, an active mutate form of the epidermal growth factor receptor, is also a notable CAR-Target because it is frequently found in GBM but absent in other tissues. In 2017, investigators had reported an EGFRvIII CAR-T cell therapy for relapsed GBM.[5] In this study, ten patients with recurrent EGFRvIII-positive GBM had received a single intravenous infusion of autologous anti-EGFRvIII CAR-T cells. There was no cytokine-release syndrome or neurotoxicity event reported. One of these patients had disease stabilization lasting over 18 months after treatment. In this trial, seven patients underwent surgical resections of the tumor after CAR-T cell infusion. The post-treatment biopsy showed decreased tumor EGFRvIII expression and with upregulation of some immunosuppressive factors, including Indoleamine 2,3-dioxygenase 1 and programmed cell death ligand 1. They also found the numbers of regulatory T cells in the tumor were increased. Based on these results, this study demonstrated that the CAR-T cells can cross the blood-brain barrier and modulate the immune response in the tumor microenvironment.

2.3. Human epidermal growth factor receptor 2

HER2 is also a cell surface protein that actively targeted in various cancers including GBM. Ahmed et al[17] have shown that HER2 CAR-T cells have potential anti-cancer activity in preclinical xenograft models of GBM. However, there were safety concerns after the death of one patient.[18] Therefore the group developed a new generation of HER2 CAR with an FRP5 (a recombinant of

HER2 antibody; Creative BioLabs Inc., Shirley, NY, USA) ectodomain and a CD28z endodomain. The new clinical trial including 17 patients with progressive HER2-positive GBM received one or more infusions of autologous HER2 CAR-T. No dose-limiting toxicity was noted after T cells infusions. During follow-up, the number of HER2 CAR-T cells did not expand but could be detected in the peripheral blood for up to 12 months after the infusion. The reported median overall survival was 11.1 months after infusion and 24.5 months after diagnosis. Half of the patients had clinical benefit (one partial response and seven stable).

2.4. Ephrin type-A receptor 2

EphA2 belongs to a family of the Eph receptor tyrosine kinases. It is frequently overexpressed in kinds of malignancies, including GBM.[10,19] Expression of EphA2 contributes to cell proliferation, migration, and invasion and is correlated with poor prognosis.[20,21] Previous studies had generated a panel of EphA2-specific CARs and that resulting in potent anti-cancer activity in a preclinical glioma xenograft model.[22]

2.5. B7-H3 (CD276)

Recently, the antigen B7-H3 (a type 1 transmembrane protein, also as an immune checkpoint molecule) had been reported broadly which is overexpressed by multiple cancer cells, such as medulloblastoma and diffuse intrinsic pontine glioma in children.[23] Therefore it has been suggested to be a possible candidate target for CAR-T therapy to treat brain tumors. The specific antitumor functions of B7-H3-specific CAR-T cells had confirmed by cytotoxic and enzyme-linked immunosorbent assay assay both in primary GBM cells and cell lines. The xenograft orthotopic GBM model also showed a significantly longer median survival in CAR-T cells treated group than control group.[8]

3. THE OBSTACLES OF CAR-T IMMUNOTHERAPY IN GBM

Unlike the enormous impact of CAR-T cell therapy has seen in B-cell lymphoma, the response in GBM patients has been unassuming at best. It is important to note, recent clinical trials of CAR-T therapy suggest that the engineered T cells can be activated and infiltrate into the malignant tissue. However, there are many studies showed insufficient anti-tumor activity.[24] The major challenges for CAR-T cell immunotherapy in GBM include lack of specific tumor target antigens, tumor heterogeneity, inadequate CAR-T cell trafficking to tumor sites, T cell exhaustion (intrinsic T cell dysfunction) and the immunosuppressive microenvironment (extrinsic T cell dysfunction) of central nervous system (CNS) tumors.[25] These barriers have limited the current CAR-T cell treatment in GBM.

3.1. Low/lost and heterogeneous antigen expression

GBM is highly heterogeneous and grows rapidly. This tumor presents invading and infiltrating neighboring normal brain tissues. It is not only making complete tumor resection difficult but also becomes imperative to expand the potential to identify additional GBM-specific antigens. Because of the variation in antigen expression among heterogeneity, a patient base tailored target selection will be necessary. Furthermore, even after the successful CD19-CAR-T treatment of the B-cell malignancies, patients often relapsed the disease without detectable CD19 antigen.[3,4] The phenomenon of loss or decrease in target antigen expression is more often observed in clinical studies of brain tumors. Brown et al[3] had reported that IL13Rα2 decreased presentation in recurrent tumors after CAR-T therapy. The further advancing CAR-T therapy requires some strategies to minimize the tumor heterogeneity that causes the antigen to decrease or loss. The strategy of multiple targeting therapies may be attempted. A new trial with a combination of EGFRvIII CAR-T cells with pembrolizumab (anti-PD-1 antibody) is currently on the way (NCT03726515).

3.2. Intrinsic/extrinsic T cell dysfunction and immunosuppressive microenvironment of CNS

One of the challenges is the ability of tumor inhibition to T cell activity.[26] The effect of immunosuppression has been demonstrated by impaired cellular immunity in patients with GBM and murine models.[27] The mechanisms of these immunologic effects are not completely defined but seem to involve both tumor-intrinsic factors and host responses to tumor antigens originating from the CNS. For example, Jackson et al[28] found that the CNS melanoma may impair the systemic antitumor immunity. In mice animal models, when melanoma cells with a neoantigen expression were implanted into the brain, some antigen-specific T cells were actively deleted. The T cells which escaped the deletion also decrease the pro-inflammatory cytokines secretion and cytotoxic functions.[28] This tumor-related immune suppression may be hypothetically mediated by transforming growth factor beta (TGFβ, an immunosuppression cytokine) which secreted by microglia within the tumor microenvironment. The serum TGFβ level was elevated in the brain tumors group than the control group. The use of a TGFβ inhibitor (Galunisertib) partially increased the number of T cells but did not affect the overall survival.[28] However, Chang et al[29] developed a new generation of CAR consisting of single-chain fragment variable TGFβ neutralizing antibodies. The neutralizing of TGFβ caused the activation and stimulation of CAR-T cells. Mohammed et al[30] also designed the CAR-T cells with fused of interleukin (IL)-4 receptor ectodomain and IL-7 receptor endodomain. The IL-4/IL-7 CAR-T cells neutralized the IL-4 cytokine (an immunosuppression cytokine), promoted cell proliferation, and anti-tumor ability in vivo. The environmental cytokines that inhibited myeloid cells also associated with immunosuppression. Bloch et al[31] found that the peripheral blood macrophages of GBM patients express increased levels of programmed cell death ligand 1, which activated the immune checkpoint receptor to restrict the activity of T cells. The combination of therapies to overcome the hostile environment may be a strategy to improve the T cell function. Some in vitro studies have shown the possible benefit of PD-1 blockade in murine glioma models.[32] The unique biology of GBM and its microenvironment may be different from general T cell biology. It is important to increase our understanding of the CNS immune environment for designing a CAR-T cell treatment strategy.

3.3. Insufficient T cell trafficking

The blood-brain barrier is a unique limitation in the CNS which restricts the T cells enter into the brain. Additionally, in the case of GBM, the tumor necrosis leads to an area of hypoxia and causes immunosuppression.[33] It is unknown if CAR-T cells will be able to sustain their anti-cancer ability when exposed to an immunosuppressive microenvironment. Strategies specifically tailored to the unique CNS environment may thus be needed to develop CAR-T cells for gliomas. Some local/regional delivery methods including intratumoral and intraventricular administration are developing to overcome the anatomical barriers involved in T cells trafficking. Local/regional delivery of CAR-T cells also reduces the risk of systemic toxicities by decrease the number of therapeutic cells.

4. CONCLUSION AND PERSPECTIVE

The CAR-T immunotherapy is a revolution option for cancer treatment. The therapy had made a dramatic response in the

treatment of hematologic malignancies. However, brain tumors still are considered difficult to succeed. According to the recent clinical experiences, we have known that the tumor heterogeneity, lock of an ideal and universal target, CAR-T cell exhaustion, insufficient tumor trafficking, and immunosuppressive microenvironment are major obstacles of CAR-T therapy. To advance understand neuro-immunology will help to treat GBM more effectively. The ongoing studies have many approaches including a combination of immunotherapy and other standard treatment such as chemotherapy or target therapy may become the best resort for improving outcomes. In the future, we may make a personalized, targeted approach based on the molecular and genetic profile which can suit every individual to reduce the side effects and give a hope of improving clinical outcomes.

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