Proceedings of the 6th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/2026.38098

Combination Therapies of CAR-T Cells for Glioblastoma: Current Advances, Challenges, and Future Perspectives

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Abstract. Glioblastoma multiforme (GBM) is one of the most aggressive malignant brain tumours among adults. Since many conventional therapies have demonstrated limited advancement, an emerging immunotherapy called Chimeric Antigen Receptor T-cell therapy (CAR-T therapy) is gradually becoming the hope for transforming GBM treatment. However, due to intrinsic limitations, such as the immunosuppressive tumour microenvironment (TME), heterogeneity of tumour cells, antigen escape, and the blood-brain barrier (BBB), CAR-T monotherapy has also shown unexpected preclinical results. To enhance drug efficacy and overcome related challenges, many researchers have combined CAR-T therapy with other therapeutic approaches. As a result, this review focuses on the mechanisms and strengths of four distinct combination treatments with CAR-T therapy in GBM, including chemotherapy, radiotherapy, immune checkpoint inhibitor (ICI) therapy, and oncolytic virus (OV) therapy. This review concludes that these combination therapies could improve the proliferation, persistence, and infiltration of CAR-T cells, achieving higher efficacy. Nevertheless, the radical problems, like the TME and heterogeneity, remain unsolved. In summary, this review aims to provide a general idea about CAR-T combination therapies from the mechanisms, strengths, and limitations. Future research can focus on developing more late-stage clinical trials or modifying the structures of CAR-T cells.

Keywords: CAR-T cells, Glioblastoma, combination therapy, immunotherapy, tumour microenvironment

1. Introduction

Glioblastoma multiforme (GBM) accounts for 49% of malignant brain tumours and is considered one of the most prevalent and aggressive tumours among adults [1]. The current Food and Drug Administration (FDA)-approved treatments for GBM consist of surgical resection, chemotherapy with temozolomide (TMZ), radiotherapy, and tumour-treating fields (TTFields). Although traditional therapeutic methods have achieved certain results over the past two decades, the overall prognosis and treatment response of GBM patients remain poor, and the median survival rate is only around 20.5 months [2]. Due to the ineffectiveness of current treatments, a new therapeutic strategy is urgently required to treat GBM.

Fortunately, an emerging immunotherapy has revolutionized the treatment of multiple tumours and provides hope for the development of GBM treatment. This therapy is called Chimeric Antigen

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DOI: 10.54254/2753-8818/2026.38098

Receptor T-cell therapy (CAR-T therapy) and has become well-known for its unprecedented achievement in haematological malignancies. For example, after applying CAR-T cell therapy to treat refractory large B-cell lymphoma, around 82% of cases showed a response and 54% of patients achieved a complete response, illustrating that this therapy has an outstanding effect in curbing tumour growth [3]. Owing to its potential, researchers have shifted focus from haematological tumours to solid tumours, including GBM.

The reason why CAR-T therapy could achieve such a compelling result among haematological tumours is due to the special structure of the receptors. To be more specific, CAR-T cells are cytotoxic T cells, which are extracted and genetically modified ex vivo to express a CAR. CARs enable the cells to bind a tumour antigen (TA) specifically and directly without the need for MHC [4]. By contrast, all natural cytotoxic T cells' activity is dependent on the presence of MHC; therefore, CAR can prevent immune escape of tumour cells.

Although CAR-T therapy is expected to transform GBM treatment, there are many obstacles hindering its development in clinical trials. Firstly, CAR-T cells find it hard to migrate to the tumour site, because the blood-brain barrier (BBB) acts as a selective barrier, preventing them, as well as harmful substances, from reaching the brain. In addition, CAR-T therapy inevitably carries the risk of developing inflammation and severe toxicity, involving cytokine release syndrome (CRS) and central nervous system (CNS)-specific complications. Moreover, after patients are treated with CAR-T therapy, drug resistance and tumour relapse may occur, because of antigen escape, tumour heterogeneity, and an immunosuppressive tumour microenvironment (TME).

Since CAR-T therapy exhibits limited capacity to fully perform its function in clinical trials, more researchers intend to improve its effectiveness by combining it with other therapeutic approaches. To begin with, chemotherapy with the small-molecule drug temozolomide (TMZ) is widely used in promoting proliferation of CAR-T cells and maintaining their long-term survival. Meanwhile, low-dose radiotherapy (RT) can not only enhance the expansion and activity of CAR-T cells but also overcome tumour heterogeneity. Compared to the traditional methods in GBM treatment, emerging immunotherapies could also be prospective candidates in combinatorial treatment. For instance, immune checkpoint inhibitors (ICIs) may mitigate CAR-T cell exhaustion and immune suppression. Furthermore, oncolytic viruses (OVs) are great adjuvants because they can reprogramme the TME and address antigen escape.

In summary, this review aims to outline the mechanisms of four different combination therapies with CAR-T treatment. It will consist of chemotherapy, radiotherapy, ICI therapy, and OV therapy. Additionally, to further optimise the given combination therapies, the evaluation of the strengths and limitations of respective strategies is summarised.

2. Combination with chemotherapy

Chemotherapy treats cancer by inhibiting or impairing essential cellular mechanisms, like DNA replication and cell division; however, it targets both tumour and rapidly dividing cells, leading to severe side effects. As lymphocytes divide and differentiate frequently, TMZ molecules tend to induce lymphodepletion, then prompting the expression and release of cytokines IL-7 and IL-15. Since there are fewer endogenous lymphocytes competing for these cytokines, CAR-T cells can receive more pro-inflammatory signals, leading to the proliferation and persistence in circulation [5].

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3. Combination with radiotherapy

RT is a cancer treatment that uses high-energy ionising radiation to damage tumour cell DNA, causing the cell cycle to stop or inducing apoptosis. Many papers have investigated how RT can synergize with CAR-T cell treatments and concluded that RT can address heterogeneity, improve cell migration, and trigger cell proliferation. For example, the research paper of the DeSelm team indicated that cells with negative antigens can respond to TNF-related apoptosis-inducing ligand (TRAIL) after being subjected to RT intervention [6]. This finding is significant for solving the problem of heterogeneity, because antigen-negative tumour cells can also be eliminated by TRAIL-mediated apoptosis after antigen-positive tumour cells activate CAR-T cells to release TRAIL. Besides, animal experimental evidence obtained by the Murty team demonstrated that RT is a key factor in enhancing the local vascular permeability at the tumour sites. This facilitates the infiltration of immune cells, therefore stimulating rapid proliferation and enhancing drug delivery efficiency [7]. Additionally, Sampson's team discovered that RT could result in the clearance of lymphocytes, thereby using the increased pro-inflammatory cytokine levels to maintain the activity and survival of cells in the TME [8].

4. Combination with immune checkpoint inhibitor

Under normal conditions, body cells express specific antigens to bind and inhibit leukocytes, with the aim of preventing their over-activation and autoimmunity. However, tumour cells exploit this self-defence mechanism and overexpress the surface antigens for immune evasion. Therefore, by utilising complementary antibodies to disrupt inhibitory immune checkpoint axis, immune cells, including CAR-T cells, can ideally overcome immune suppression and improve drug efficacy. Following this, this section will introduce three emerging ICIs that are designed to overcome different CAR-T monotherapy limitations.

4.1. Anti-egfrviii-sgrp CAR-T cells

This combination therapy primarily focuses on resolving two CAR-T therapy limitations: immune suppression and tumour heterogeneity.

Unlike haematological cancers, GBM solid cancers exist within an immunosuppressive TME. TME consists of many suppressive factors which can undermine immune cells' sensitivity and function. The dominant immune cell populations of GBM are glioma-associated microglia and macrophages (GAMs). Their activity is largely weakened, because tumour cells can overexpress CD47 cell surface receptors and co-opt the CD47-signal regulatory protein alpha (SIRPa) axis to evade the immune response [9]. To revive the function of GAMs, a CAR-T cell therapy called anti-EGFRvIII-SGRP was designed as an innovative solution. Once the epidermal growth factor receptor (EGFR) variant III (EGFRvIII) is identified, the cytotoxic T cells will activate the secretion mechanism of signal regulatory protein gamma (SIRPγ)-related protein (SGRP) [9]. As SGRP has a higher affinity for CD47, CD47 prioritizes binding to SGRP over SIRPa, thereby blocking the inhibitory signalling pathways of GAMs [9]. To sum up, ICIs enhance therapeutic effects by reducing the impact of the TME and restoring the anti-tumour phagocytic function of GAMs.

Tumour heterogeneity is the primary driver of drug resistance. Thanks to the hypoxia gradients and uneven distribution of pro-inflammatory factors, glioma stem cells (GSCs) are triggered by different stresses and later differentiate into different subclones. Some of the subtypes can evade the CAR-T immune response via the process called antigen escape, which is achieved by

DOI: 10.54254/2753-8818/2026.38098

downregulating or mutating the targeted antigens [10]. In this case, EGFRvIII-negative GBM cells cannot be detected by the given receptors, providing a chance for some tumour cells to survive and recur. The reactivation of GAMs becomes a breakthrough in addressing tumour heterogeneity, because GAMs belong to the innate immune system, in which GAMs can target and engulf tumour cells with different antigens [9]. Consequently, this combined treatment can effectively alleviate the phenomenon of immune evasion and prevent GBM from developing a drug-resistant phenotype.

4.2. PD-1/PD-L1 axis blockade

PD-1/PD-L1 axis consists of the programmed cell death protein-1 (PD-1) receptor of T lymphocytes and programmed cell death-ligand 1(PD-L1) antigens of GBM tumour cells. When CAR-T cells are disturbed by the TME, the continuous activation mechanism will cause the expression level of the mentioned receptors to increase. When this axis occurs, Src homology 2 domain-containing phosphatase 2 (SHP-2) will be recruited and dephosphorylate key T cell receptor (TCR) signalling molecules [11]. As a result, the TCR signalling pathway is disrupted, and cells progress to T cell exhaustion [11]. Since cells enter a state of exhaustion, their proliferative potential is restricted, the scale of cytokine release decreases, and their cytotoxic ability also declines. To address these issues, many researchers have begun to combine CAR-T treatment with PD-1 inhibitors. The preclinical data illustrated that this ICI could enhance the cytotoxicity of tumour-infiltrating lymphocytes (TILs) and anti-EGFRvIII CAR-modified T cells [12]. In addition to high efficacy, this combined therapy exhibits high safety. This is shown in a recent phase I trial (NCT03726515), where 7 patients who received the given combinatorial drugs with the PD-1 inhibitor pembrolizumab showed no observed dose-limiting toxicities [13].

4.3. Gene editing and silencing strategies

With the increasing advancement of gene-editing technology, many research groups have attempted to combine gene-editing tools with CAR-T treatment, aiming to create a long-lasting efficacy of the drug. Owing to the high potency and ease of use, clustered regularly interspaced short palindromic repeats-CAS9 ribonucleoprotein (CRISPR-CAS9) has become the primary choice. In research conducted by Rupp et al, CRISPR-CAS9 is used to remove the gene coding for PD-1 checkpoint receptors in CAR-T cells [14]. The deletion of receptor proteins destroys the axis, allowing the TCR signalling pathway to function normally and preventing T cell exhaustion. Similarly, some researchers utilize the RNA interference (siRNA) tool to silence the PD-1 gene and degrade its corresponding mRNA, preventing the mRNA from translating into the PD-1 receptor protein [15] .Although these combination therapies have achieved some results, their potency and safety for GBM in clinical trials haven't been validated yet.

5. Combination with oncolytic virus

OVs are a group of naturally occurring or genetically engineered viruses that can identify, replicate and lyse the targeted tumour cells. Apart from that, the lysed tumour cells could release potent signalling molecules, such as damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs) and tumour antigens. These molecules then trigger both anti-tumour innate and adaptive immune systems, resulting in the increased immune response with long-term effects.

DOI: 10.54254/2753-8818/2026.38098

A lot of CAR-T treatments fail to achieve the expected clinical outcomes owing to the TME and insufficient infiltration. Therefore, some researchers have tried to combine OVs with CAR-T treatments, intending to leverage the advantages of OVs to improve the cytotoxicity and expansion of leukocytes.

5.1. CXCL11-armed oncolytic adenovirus

Wang el al. research team found that T cells naturally express high levels of the CXCR3 receptor, and the transwell assay demonstrates that CXCL11 is a potent chemoattractant to these cells [16]. Thus, the research group engineered the OVs to form CXCL11-armed oncolytic adenovirus (oAd-CXCL11), aiming to use released CXCL11 to attract cytotoxic T cells to the tumour location after the engineered viruses infect the tumour. To validate that this OV can enhance the infiltration of B7H3.CAR-T cells, researchers conducted a series of in vitro experiments. For example, in vitro migration assays confirmed that the migration ability of modified T cells in the cell population infected with the given OV was stronger than that of the control group [16]. Moreover, in vitro infiltration assays verified that tumour spheroids of U87-mCherry cells infected with OVs showed greater migration of modified T cells [16]. Apart from that, both 2D and 3D co-culture assays indicated that combined approaches induced greater efficacy against GBM (16). Besides, the research demonstrated that combination treatment can increase the infiltration of CD8+ T lymphocytes, natural killer (NK) cells, and M1-polarized macrophages, while decreasing the proportions of myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs) and M2-polarized macrophages [16]. This is because OVs-induced immunogenic tumour cell death increased the antigen availability and the release of cytokines and chemokines, thus activating and attracting other immune cells. Overall, it is reliable that oAd-CXCL11 has the ability to reprogram the immunosuppressive TME and enhance infiltration of immune cells.

5.2. OVV-03 oncolytic virus

Tang et al engineered OVs to form OVV-03, derived from the vesicular stomatitis virus (VSV) and inserted with HER2 transgene. Owing to the ability to address tumour heterogeneity, remodel TME and synergize with both B7H3-targeted and HER2-targeted CAR-T therapies, OVV-03 is regarded as one of the potent adjuvant strategies in enhancing the efficacy of CAR-T treatment against GBM.

TME takes primary role in inducing T cells to develop exhaustion. OVV-03 can remodel the TME, thereby sustaining and prolonging the therapeutic effects. It achieves the goal in two ways – inducing direct oncolysis and suppressing immune checkpoint pathways. From Annexin V/propidium iodide (PI) staining experiments, this OV infection increased the apoptotic cell populations in both GBM cell lines and patient-derived GBM cell lines, illustrating that it has the capacity to overcome apoptotic resistance among GBM cells [17]. In addition to enabling tumour cells to progress to cell death, this OV can suppress the clonogenic capacity of tumour cells by inhibiting proliferation and eliminating GBM subpopulations that trigger tumour recurrence, thereby alleviating the burden on immune systems [17]. Moreover, the treatment of OVV-03 can significantly increase the total infiltration of white blood cells within TME, such as CD45+ leukocytes, CD45+CD3+ T lymphocytes and primarily CD8+ cytotoxic T lymphocytes, therefore transforming cold tumours to hot tumours [17]. Additionally, OVV-03 can suppress the JNK-c-Fos/c-Jun signalling pathway, indirectly down-regulating the expression of PD-L1, leading to the reduction of T-cell exhaustion [17].

DOI: 10.54254/2753-8818/2026.38098

Another special mechanism of OVV-03 is that it upregulates the expression of HER2 antigens on GBM, thus enhancing the recognition of corresponding CAR-T cells [17]. Since the OV demonstrates a potent synergy with two types of receptors, the combination therapy can decrease the frequency of developing antigen escape and drug resistance caused by heterogeneity.

6. Discussion

6.1. Combination with chemotherapy

While lymphodepletion can ideally increase the proliferation and persistence of CAR-T cells in circulation, it may concomitantly bring lymphopenia, reducing the number of lymphocytes to an abnormal level. This is because chemotherapy with TMZ is a non-selective treatment, which can target and damage both cancer cells and endogenous lymphocytes. Once lymphopenia is severe, chemotherapy with TMZ will become detrimental to the health of the patients and largely undermine the efficacy of CAR-T treatments, eventually outweighing the benefits it brings for combination therapy. For example, patients with lymphopenia and neutropenia will have a weaker immune system, making them more vulnerable to opportunistic diseases and infections. This suggestion is supported by the investigation conducted by Rejeski et al. This research team summarised clinical outcomes from 248 patients receiving standard-of-care CD19 CAR-T and concluded that the infection risk was increased by prolonged neutropenia [18]. Furthermore, excessive elimination of lymphocytes results in a reduced level of cytokine secretion, which in turn indirectly suppresses the expansion of CAR-T cells. This outcome counteracts the positive impact of lymphodepletion, leading to the unexpected clinical results. To make matters worse, the death of numerous lymphocytes may lead to an excessive inflammatory reaction, aggravating the risk of having CRS and CNS-specific complications. Apart from that, since TMZ eliminates cancer cells by destroying DNA structure, the genetic instability may induce tumour hypermutation, facilitating the development of resistance and antigen escape. As a result, chemotherapy with TMZ is a double-edged sword. An appropriate dose of it can enhance the expansion and proliferation of CAR-T cells, whereas an excessive dose may impair the immune system, introduce toxicity, and backfire by promoting tumour resistance. Moreover, considering that there are few papers describing the results of combined therapy in the clinical phase, in the future, more experiments need to be conducted to verify the safety and efficacy. It is also important to measure and test the dosage and administration schedule of combined drugs, because it directly affects the effectiveness of drugs.

6.2. Combination with radiotherapy

Radiotherapy is not a tumour-specific therapy. While it increases infiltration and proliferation of CAR-T cells, it inevitably causes some lymphocytes and CAR-T cells to progress to the apoptotic stage, thereby reducing the potency of the immune response. Besides, numerous studies demonstrate that the efficacy of CAR-T treatment is highly correlated with the dose of RT. It is believed that low doses of 2 Gy of radiation promote the formation of an immunogenic tumour microenvironment; however, high doses of 5–10 Gy may inhibit the infiltration and migration of CAR-T cells via inducing vascular injury and reducing the secretion of chemoattractants [2]. What is worse is that intense vascular damage and the regional death of tumour cells may accelerate the formation of hypoxic regions, leading to the development of necrotic regions and intensifying the immunosuppressive effect of TME. Additionally, while the pro-inflammatory cytokines stimulated by RT can cause the proliferation of T cells, they can also sustain the survival of Tregs. Tregs are

DOI: 10.54254/2753-8818/2026.38098

immunosuppressive CD4+ T cells whose normal fuction is to restrain immune activity; therefore, the increased level of Treg cell recruitment within the tumour region contributes to the enhanced TME, decreased cytotoxicity of CAR-T cells and the development of T cell exhaustion. The high-level expression of pro-inflammatory cytokines can also promote persistent inflammation within the tumour sites, especially the necrotic region, which will be lethal for GBM patients. Besides, increased vascular permeability is not exclusively beneficial. The reason is that the excessive extravasation of fluid from blood vessels will increase the risk of local cerebral edema and elevated intracranial pressure, which physically slows down the blood flow rate and deteriorates the hypoxic impact. Apart from that, increased vascular permeability can also facilitate the invasion of malignant tumour cells, permitting GBM infiltration into different tissues. Although combination therapy with RT can eliminate partial antigen-negative cells, it cannot utterly resolve the issue of heterogeneity due to the heterogeneous GBM distribution. As RT cannot evenly sensitise all the heterogeneous GBM, the GBM tumour still consists of spatially or temporally resistant tumour populations, thus allowing antigen escape and tumour recurrence. Similarly, this combination therapy for GBM treatment has only achieved limited clinical results in early-phase trials, restricting the generalizability of the outcomes. Therefore, more clinical trials should be conducted to verify the dosage standard with greater accuracy.

6.3. Combination with immune checkpoint inhibitor

While ideally ICI has the greatest potential to address the problems of tumour heterogeneity and T cell exhaustion, the real TME is more complicated and blocking one inhibitory pathway usually is not sufficient to thoroughly solve the issues. For example, in the drug with anti-EGFRvIII-SGRP CAR-T cells, CAR-T cells have to recognise the EGFRvIII antigen on GBM tumour cells before secreting SGRP proteins to stimulate GAMs' immune response; however, if the tumour cells are EGFRvII-negative or lose antigens, CAR-T cells cannot efficiently identify them, consequently leading to tumour escape. Furthermore, as CD47 is also expressed on normal red blood cells, this ICI may cause off-tumour toxicity and haemolytic anaemia. Moreover, checkpoint blockade cannot fully reverse T cell exhaustion. T cells have multiple inhibitory signalling pathways and corresponding receptors, rather than only having one pathway, such as the PD-1/PD-L1 pathway. Consequently, after PD-1 is blocked, T cells may upregulate other antigens to maintain T cell exhaustion. Besides, chronic antigen stimulation triggers exhausted T cells to undergo stable epigenetic and transcriptional changes. The reprogramming will enforce T cells to stay exhausted, even if the PD-1/PD-L1 pathway is blocked. In addition, immunosuppressive GBM TME can continue inhibiting CAR-T cells even after checkpoint blockade, so ICIs have limited efficacy for GBM treatments. The gene editing and silencing strategies also have limitations. The irreversible genetic modification carries the risk of developing off-target mutations, and the permanent removal of the PD-1 gene tends to cause autoimmune and uncontrolled inflammation. To minimise the effect of T cell exhaustion, researchers could design multiple checkpoint inhibitors or insert numerous chimeric antigens on CAR-T cells, therefore preventing reliance on a single inhibitory pathway.

6.4. Combination with oncolytic virus

Although OVs can release chemoattractants to improve the infiltration of CAR-T cells, OVs must target and infect tumour cells before lysing them and releasing signalling molecules. However, GBM cells are spatially heterogeneous. Thanks to that, some antigen-negative cells have the ability to evade direct oncolysis from oncolytic viruses and extermination via attracted immune cells.

DOI: 10.54254/2753-8818/2026.38098

Another reason why drug resistance and tumour relapse still occur in this combination therapy is that the clonogenic suppression is transient. This is because suppressing clone formation cannot fully eradicate cancer stem cells, which will survive and re-establish the tumour population. Additionally, patients with a less immunosuppressive TME express a weaker response to this combination therapy, because the host immune system can efficiently eliminate the OVs before the viruses spread throughout the tumour region. Meanwhile, due to the excessive release of cytokines or other inflammatory mediators, the CAR-T therapy combined with OVs also encounters the issue of systemic inflammation and the risk of CRS. Moreover, chemoattractants are not specific. While they attract numerous immune cells to enter the tumour region and remodel the TME, they may also inadvertently recruit Tregs or MDSCs, which potentially counteracts the desired reduction in immune suppression. It is important that not all the immune cells attracted are beneficial in transforming TME. For instance, after macrophages enter the tumour site in the brain, they may be polarized and transformed into an M2-like phenotype, thereby becoming immunosuppressive cells. In addition to the limitations related to the TME, BBB is still an unsolved problem that can hinder immune cells, including CAR-T cells, from entering the tumour region inside the brain; however, there are few papers explaining the correlation between the dosage of drugs and the availability of CAR-T cells crossing the BBB, so more clinical studies should be conducted.

7. Conclusion

This review summarises the mechanisms of four different combination therapies for CAR-T therapy in GBM treatment, including chemotherapy, radiotherapy, ICI therapy and OV therapy. Furthermore, this review analyses how each combinatorial therapy can assist CAR-T treatment via either improving its efficacy or overcoming the major limitations of CAR-T monotherapy. Apart from that, it evaluates the current obstacles of four combination treatments and provides an outlook on how these drawbacks may be addressed. This review aims to provide comprehensive information about CAR-T combination treatment, facilitating researchers to understand the general aspects of emerging combination therapies, current limitations, and future improvements. Although these combinatorial treatments can improve the persistence, proliferation and infiltration of T cells, the fundamental challenges, such as heterogeneity, antigen escape, TME, and tumour resistance, remain unresolved. In addition, the conclusions about each treatment's efficacy and safety are premature. The reason is that many CAR-T combination strategies in GBM are merely supported by preclinical trials, while most of the clinical trials stop at the early phase. In the future, researchers should move beyond single-antigen CAR-T cells towards multi-antigen CAR-T cells, decreasing the probability of antigen escape. Besides, researchers can engineer CAR-T cells and generate, for example, checkpoint-resistant or cytokine-secreting types. Ultimately, the efficacy of drugs is dependent on the dosage, so more clinical trials should be conducted to test the optimum dosage.

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