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The Role of Immune Checkpoint Inhibitors in the Treatment of Glioblastoma: A literature Review of Current Evidence

Marwan Jaber[1], Lizi Dzhodzhua[2], Hammad Khan[3], Mariam Abdelghani[4], Eman Aburas[5]

[1]Faculty of Medicine, University of Georgia, Tbilisi, Georgia; [2]Faculty of Medicine, Caucasus University, Tbilisi, Georgia; [3]Faculty of Medicine, Tbilisi State Medical University; [4]Faculty of Dentistry, New Vision University; [5]Faculty of Dentistry, New Vision University

***Corresponding author:* Marwan Jaber, Faculty of Medicine, marwanmjaber@gmail.com, +995595127118.

***ORCID:* 0009-0008-9658-6136[1], 0009-0003-1550-0008[2], 0009-0001-9681-0424[3], 0009-0003-2516-9494[4], 0009-0004-1398-8246[5]

Abstract

Background: Immune checkpoint inhibitors (ICIs) have shown promise in the treatment of many cancers but have faced many challenges in treating glioblastoma (GBM) due to the tumor's unique immune microenvironment.

Methods: This literature review was conducted to explore the role of ICIs in GBM, focusing on PD-1 and PD-L1 inhibitors, and their potential in combination therapies. Studies were retrieved from PubMed, Web of Science, and a total of 26 articles were included for data extraction after applying inclusion and exclusion criteria.

Results: ICIs in GBM has demonstrated limited clinical benefit despite the strong biological rationale. Large phase III trials showed that PD-1 inhibition with agents like nivolumab has not improved overall or progression-free survival, largely due to the tumor heterogeneity, immunosuppressive tumor microenvironment, and low tumor mutational burden. CTLA-4 inhibitors like ipilimumab and tremelimumab have shown limited efficacy as monotherapy, though combination or salvage strategies following failure of PD-1 showed some results, particularly in replication-repair–deficient or hypermutated gliomas. Standard chemoradiotherapy with temozolomide remains the standard of treatment, with MGMT promoter methylation as the strongest predictive biomarker. Adn PD-L2 remains underexplored as a target.

Conclusion: Overall, the evidence shows that monotherapy with ICIs is insufficient in GBM, and future approaches for these agents will require case-studied patient selection, combination strategies, and integration with existing standard therapies.

Keywords: Glioblastoma, PD-1 inhibitors, PD-L1 inhibitors, PD-L2 inhibitors, CTLA-4 inhibitors, overall survival, progression free survival.

Introduction

Glioblastoma (GBM) is the most common and aggressive primary malignant brain tumor in adults, with a very poor prognosis and a median overall survival (OS) of approximately 15 to 17 months. GBM is highly invasive, exhibits rapid growth, and recurs in virtually all patients, with a 5-year OS rate of less than 10% (15).

The statistic hasn't changed much in decades about glioblastoma multiforme (GBM), and its difficulty to treat. One area of hope has come from immunotherapy or immune checkpoint inhibitors (ICIs) These drugs are designed to help the body's own immune system recognize and fight cancer. They've made a huge difference for patients with other cancers like melanoma and lung cancer. Naturally, researchers began asking if they could they help people with GBM. However, the brain's immune environment is different, it's tightly controlled, to protect brain cells, meaning immune responses are often dampened. On top of that, GBM creates a microenvironment that blocks immune attacks, shuts down T-cells, and hides from the immune system. So even though ICIs should help, they haven't been as successful in GBM as they've been in other cancers (3, 8). That said, the story is still unfolding. This review takes a closer look at where things stand with ICIs in GBM. What's working and what's not, and what might be coming next. We explore how these drugs interact with the tumor's biology, what clinical trials have shown, and how they might play a stronger role in the future especially when combined with other treatments. While ICIs haven't been a silver bullet, they still hold promise and, in a disease, as tough as GBM, even small steps forward matter a lot.

Methodology

This narrative literature review was conducted to explore and synthesize the role of Immune checkpoint Inhibitors in the treatment of glioblastoma.

The articles were gathered and organized from PubMed and Web of Science. The search was conducted using combination of keywords: "Immune Checkpoint Inhibitors", "Glioblastoma", "High Grade Glioma".

Boolean operators such as AND, OR, NOT were used to increase the precision of the search. The study focuses mainly on patients with glioblastoma that are treated with Immune Checkpoint Inhibitors with or without chemoradiotherapy or surgery.

Inclusion criteria

Review studies randomized and non-randomized clinical trials. Articles published in English.

Exclusion criteria

Animal Studies or Preclinical trials, non-English studies, case reports and case-studies, non-peer reviewed studies, studies not related to glioblastoma, studies lacking clear relevance to the role of immune checkpoint inhibitors in glioblastoma treatment.

Title and abstract screening was done, followed by full text screening. In disagreements between reviewers, consensus was reached with the help of a third reviewer. After applying the inclusion and exclusion criteria, a total of 26 articles were included in this review.

Results

PD-1

Programmed cell death protein 1 (PD-1) is a key immune checkpoint receptor found on activated T cells. It helps regulate T cell activity and prevent excessive immune responses. In glioblastoma (GBM), PD-1 expression is increased on tumor-infiltrating lymphocytes (TILs), which contributes to T cell dysfunction, weakening their ability to fight the cancer and allows the tumor to avoid immune detection. Treatments that block PD-1 with special antibodies aim to restore T cell activity and enhance antitumor immunity. However, clinical application of PD-1 inhibitors in GBM is a significant challenge (1,2).

Large phase III trials including CheckMate 143 compared nivolumab against bevacizumab in patients with recurrent GBM. It did not show an improvement in overall survival (OS). In fact, patients on nivolumab lived about 9.8 months on average, compared to 10 months with bevacizumab and their Progression-free survival (PFS) was even shorter with nivolumab. This suggests that tumor's natural resistance mechanisms limit its effectiveness in this setting. These disappointing results are due to glioblastoma's highly lymphocyte-depleted and immunosuppressive tumor microenvironment (TME). Promoting T cell dysfunction despite presence of PD-1-positive tumor infiltrating lymphocytes (TILs). Overall, these results show that blocking PD-1 alone is not enough to effectively treat GBM, despite a strong immunological basis (1).

Currently, we do not have reliable biomarkers to predict how well glioblastoma patients will response to PD-1 inhibitors. While PD-1-positive (TIL) density and PD-L1 expression on tumor cells have been studied, these do not consistently match up with clinical outcomes (2,3). Retrospective analyses demonstrate that about 29% of cases have PD-1-expressing TILs, but their density varies and does not reliably predict patient survival outcomes (2). This highlights how complex the immune evasion is, where strong activation of PD-1/PD-L1 pathway occurs alongside multiple overlapping checkpoints, increased numbers of regulatory TIls, and an overall immune-depleted phenotype (2,4,5). Moreover, variations within the tumor itself including differential PD-1 expression among tumor subtypes and its interaction with other immunosuppressive pathways such as the adenosine signaling make the tumor even more resistant to ICIs (5).

Genetic factors play a big role in how glioblastoma responds to immunotherapy. For example, PTEN mutations are linked to immunosuppressive tumors and poor therapeutic response (6), whereas activation of the MAPK pathway and greater variety of T cell receptors (TCRs) may help identify patients more likely to benefit (4). Another issue with GBM is the characteristically low tumor mutational burden (TMB) reducing neoantigen presentation, which further limits the effectiveness of ICIs (7).

Some gliomas with hypermutated genomes caused by replication repair deficiency (RRD-HGG) may initially respond to PD-1 inhibitors but often develop resistance over time, requiring combination strategies (8). Clinical and preclinical data suggest combining PD-1 blockers with CTLA-4 inhibitors,

radiotherapy, or other immunomodulators can improve effectiveness, but also increase toxicity risks (9,10).

Timing and strategy seem to matter a lot when it comes to using PD-1 inhibitors effectively. Evidence suggests early use before surgery (neoadjuvant therapy) seems to better activate local and systemic T cells, potentially reversing immunosuppression more effectively than adjuvant therapy alone (3,4,8,9). Additionally, combining radiotherapy, chemotherapy, or drugs targeting other pathways like the adenosine pathway may also help immune cells with PD-1 blockade, improving TIL infiltration and antitumor immunity (5,8).

PD-1 checkpoint inhibition by itself has not significantly improved the poor prognosis of GBM patients. This is largely due to complexity of tumors immune defenses, GBM heterogeneity, and the immunologically “cold” tumor microenvironment which demand multifaceted strategies. Future trials need to focus on selecting the right patients using biomarkers, tracking immune changes over time, and thoughtfully designed combination therapies (5–7).

The challenges faced by PD-1 inhibitors in glioblastoma show how difficult it is to bring immunotherapy success from other cancers into the CNS oncology setting. While monotherapy has shown limited survival benefit, ongoing research into the tumor's immune microenvironment complexity, heterogeneity, and resistance mechanisms offers hope for more personalized and effective treatments ahead. To unlock the full potential of PD-1 targeted therapies in this highly treatment resistant cancer, we will need longitudinal, biomarker driven trials and integrated immunomodulation strategies (1–10).

PD-L1

PD-1 is a protein found on the surface of T-cells. The binding of PD-L1 to PD-1 transmits an inhibitory signal that deactivates the T-cell, preventing it from attacking the cell that expresses PD-L1 (19).

The expression of PD-L1 on tumors, as assessed by immunohistochemistry, may correlate with a response to PD-1/PD-L1 inhibitors and could serve as a clinically relevant biomarker. However, systematic studies on this expression in human glioblastoma tissue samples were previously lacking.

A study by Berghoff (2014). investigated PD-L1 expression and its association with other parameters in a retrospective series of human glioblastoma samples, including both newly diagnosed and recurrent tumors. The study found that diffuse/fibrillary PD-L1 expression was present in the majority of newly diagnosed (88.0%) and recurrent (72.2%) glioblastoma specimens. The study also noted sparse-to-moderate density of TILs in most samples (72.6% of newly diagnosed cases). A key finding from this research was that PD-L1 expression and TIL density were not correlated with patient outcome. The presence of diffuse/fibrillary PD-L1 expression, or of epithelioid tumor cells with membranous PD-L1 expression, showed no impact on OS. The methylation status of the MGMT promoter was found to be a stronger predictor of patient outcome. Despite the lack of correlation with outcome, the authors concluded that because the target (PD-L1) is present in many glioblastoma samples, a clinical study with specific immune checkpoint inhibitors is warranted (5).

PD-L2

The role of PD-L2 (Programmed Death-Ligand 2),which is another PD-1 ligand is studied less but may be related to treatment resistance and immune escape, even though the PD-1/PD-L1 pathway is the main focus of immune checkpoint therapies in glioblastoma (GBM).One of the main mechanisms of immune evasion in GBM is by T-cell inhibition, that can be aided by PD-L2 binding to PD-1 receptors on T cells in the same way as PD-L1.In contrast to PD-L1, PD-L2 is more selectively expressed on dendritic cells, macrophages and occasionally tumor cells themselves rather than being widely expressed across all tumors, even with this functional overlap, the majority of published studies only address PD-L1(Zhang et al., 2020; Darvin et al., 2020; Johnson et al., 2021) [PMC7243167; PMC7682636; PMC7899692], and there is little information on PD-L2 expression levels or clinical impact in glioblastoma.

In a systematic review by Baskaran (2024), PD-L2 is included in the larger analysis of immune checkpoint targets, yet none of the trials discussed have directly targeted or measured PD-L2 expression in patients with GBM (15). However, the review notes that immune checkpoint blockade, especially with anti PD-1 agents like nivolumab, has produced limited improvement in overall survival or progression-free survival (PFS) in glioblastoma when compared to standard chemoradiotherapy regimens. This suggests that non-PD-L1 ligands like PD-L2 may contribute to the incomplete response to PD-1 inhibitors, even in cases with low or absent PD-L1 expression.

In addition, PD-L2's possible role in maintaining immunosuppressive signaling despite PD-L1 blockade could help explain the limited T-cell activation and infiltration observed in GBM tissue, as well as the modest immune-mediated effects seen in several clinical trials. Although most trials have focused on PD-L1 expression as a biomarker of response, a broader analysis of PD-1 ligand interactions including PD-L2 may be warranted to better interpret treatment outcomes. The lack of data on PD-L2 also limits current comparisons between immunotherapy plus chemoradiotherapy versus chemoradiotherapy alone, as there has been no subgrouping based on PD-L2 status in any major trials to date (15).

CTLA-4

Cytotoxic t lymphocyte-Associated protein 4, is a protein receptor found on both regulatory T cells and activated by conventional T-Cells, that helps to regulate the immune systems response. It acts as a "brake" on T cell activation, preventing the immune system from overacting and potentially attacking the body's own tissue. CTLA-4 Achieves this by binding to B7 molecules on antigen presenting cells, and it effectively competes with CD28 on another receptor on T cells for the same binding sites present and dampening the T-Cell activation. CTLA-4 on t cells signals through immunoreceptor tyrosine-based inhibitory motif (ITIM) when it binds to the B7 molecules on antigen-presenting cells, thereby suppressing overall T cell function. The main drug involved in CTLA-4 targeted is ipilimumab, which is a monoclonal antibody that block CTLA-4, preventing it from inhibiting immune responses potentially enhancing the body's ability to fight cancer (15).

Neoadjuvant therapy

Patients with high-grade gliomas and replication repair deficiency which progressed after anti-PD-1 monotherapy were treated with salvage CTLA-4 inhibitors, approximately 75% of those receiving CTLA-4 therapy demonstrated stable disease or tumour regression. 75 patients with Replication-Repair–Deficient High-Grade Gliomas (RRD-HCG) with anti PD-1 monotherapy. 20 remained progressions free after 3.7 years later. The other 55 patients later experienced progression and received further immune based salvage and CTLA-4 Inhibitors therapy due to extremely high tumor burden present. It was found out that 75% of patients receiving CTLA-4 salvage therapy showed either disease response or more stable disease and especially patients with high tumor mutation burden (TMB) benefited most. Hence the study showed that non neoadjuvant combination increased T- cell infiltration in tumor tissue, indicating stronger immune cell activation. The study observed higher CTLA-4 expression in tumors that progressed after PD-1 blockade, supporting the rationale behind adding CTLA-4 inhibitors (10).

Ipilimumab

A human IgG1 monoclonal antibody that specifically targets CTLA-4. It works by preventing CTLA-4 from binding to its ligands (eg, CD80 and CD60), thus preventing the suppression of T-Cell Activation. Ipilimumab has been used in clinical trials for various cancers, including metastatic melanoma, and is also used in combination with other therapies. It was the first FDA-Approved immune checkpoint inhibitor targeting CTLA-4 use in metastatic melanoma, with expanded approval for other solid tumors (21).

An anti-CTLA-4 monoclonal antibody in combination with nivolumab in patients with replication-repair-deficient high-grade gliomas (RRD-HCG) who had progressed after anti-PD-1 monotherapy. Notably, the combination was administered as part of a salvage strategy and in a neoadjuvant setting prior to additional treatments such as re-irradiation, tumors that progressed on prior PD-1 therapy showed increased CTLA-4, providing a mechanistic rationale for incorporating CTLA-4 blockade. The combination showed encouraging signs of improved survival and was also associated with immune-related adverse events. Hence the studies showed the use of Ipilimumab in combination with other immunotherapies had improved the conditions of the patients with glioblastoma.

CTLA-4 is located on both regulatory T cells and activated by conventional T cells that competes with the stimulatory receptor CD28 for binding to B7 ligands on antigen presenting cells, thus inhibiting T-cell activation which is useful for maintain homeostasis and preventing autoimmunity. Despites its main key role; protection; it does have its limitation (21). CTLA-4 inhibitors can't pass through the blood brain barrier, thus failing to reach the tumor. Second, the immunosuppressive microenvironment of GBM, by creating a highly an environment that’s rich in Tregs, known as regulatory T-cells, myeloid-derived suppressor cells, and inhibitory cytokines that suppresses the activation caused by the CTLA-4 blockade.

A systemic review was conducted by Schonfeld (2024) where 106 clinical trials were conducted and under investigating ICIs in glioblastoma including those targeting CTLA-4. This study mentions about the use of Monotherapies against CTLA-4 and others and shows that there is not significant improvement in glioblastoma patients. Also, it mentions about GlitlpNi trial which stands for a combination therapy trial which also did not demonstrate any significant clinical benefit or improvement. The tumor microenvironment, blood brain barrier and tumor heterogeneity plays a key role in the resistance against certain immune therapies. Overall, the articles emphasize on the challenges of using CTLA-4 blockade alone in glioblastoma and points out to ongoing efforts to improve outcomes through combination strategies (17).

Tremelimumab

A human monoclonal antibody that targets the immune checkpoint receptor CTLA-4. By binding to CTLA-4 ,Tremelimumab prevents its interaction with B7 ligands on antigen presenting cells, thereby enhancing the T-Cell activation and promoting an anti-tumor immune response. Despite its immunostimulatory mechanism, tremelimumab has demonstrated limited clinical efficacy in GBM. According to Maccari (2024), clinical trials involving tremelimumab have shown underwhelming results, largely due to immunosuppressive microenvironment nature and the intrinsic immunoresistance mechanisms within the brain. These factors contribute to overall poor T-Cell infiltration and inadequate activision, hence blunting the intended therapeutic effect (22).
The information present in the literature suggests that CTLA-4 blockade with agents like tremelimumab may require combination strategies to improve outcomes in glioblastoma. Such as, co-administration with other immunotherapies, chemotherapy or radiotherapy that may enhance immune activation and overcome tumor resistance (22). However, further clinical investigation is important to optimize such approaches and develop strategies that can significantly improve survival in glioblastoma patients.

Chemoradiotherapy

Temozolomide (TMZ) is a key chemotherapy agent used in the treatment of glioblastoma. The European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) conducted a randomized phase III trial that compared radiotherapy alone with radiotherapy plus concomitant and adjuvant temozolomide for patients with newly diagnosed glioblastoma. In the combined therapy arm of this trial, temozolomide was administered daily at a dose of 75 mg per square meter of body-surface area concurrently with radiotherapy for up to 49 days. This was followed by a four-week break, and then up to six cycles of adjuvant temozolomide at a dose of 150-200 mg per square meter for five days during each 28-day cycle. The initial results showed that the addition of temozolomide to radiotherapy significantly improved survival. The median survival was 14.6 months with the combined therapy, compared to 12.1 months with radiotherapy alone. The two-year survival rate was 26.5% for the combined therapy group versus 10.4% for the radiotherapy-

alone group. Concomitant treatment with radiotherapy plus temozolomide was associated with grade 3 or 4 hematologic toxic effects in 7% of patients {4}.

A five-year analysis of the same trial confirmed that the survival benefits of adding temozolomide to radiotherapy were sustained throughout the follow-up period. The overall survival rates for the combined therapy group were 27.2% at two years, 16.0% at three years, 12.1% at four years, and 9.8% at five years. In comparison, the radiotherapy-alone group had survival rates of 10.9% at two years, 4.4% at three years, 3.0% at four years, and 1.9% at five years. The methylation status of the MGMT promoter was identified as the strongest predictor for patient outcome and for the benefit derived from temozolomide chemotherapy {12}. It is also noted that the MGMT promoter methylation status can change between the first surgery for newly diagnosed glioblastoma and a second surgery for recurrence {11}.

Combining ICIs, such as nivolumab and pembrolizumab targeting PD-1 with chemotherapy and radiation has not significantly improved survival. The immunosuppressive tumor microenvironment of glioblastoma with low tumor mutation rate, limited neoantigen presentation and blood-brain barrier make it hard for the immune system to respond effectively (11,12). Large phase III trials combining ICIs with TMZ and radiotherapy have not shown survival improvement. (11,12).

Targeted therapies like bevacizumab have been disappointing. The NRG/RTOG 0825 trial adding bevacizumab to standard chemoradiotherapy did not help patients live longer. It revealed worsening neurocognitive function and quality of life over time in the bevacizumab group, even though their cancer took longer to progress. There is a complex balance between controlling the tumor and maintaining the patient's quality of life (13). Careful consideration of patient-centered outcomes beyond survival is important.

The ACT IV phase 3 trial evaluated rindopepimut in combination with temozolomide for newly diagnosed, EGFRvIII-expressing glioblastoma. It was noted that temozolomide-induced lymphopenia might potentially reduce the efficacy of an immunotherapy. However, this concept was not supported by the ACT II study, where patients who received dose-intensified temozolomide with rindopepimut developed a more robust immune response despite more significant lymphopenia (1).

Adding Tumor-Treating Fields (TTFs) to maintenance TMZ therapy significantly improved both PFS and OS compared to TMZ alone. On average patients lived about 21 months with the combination treatment compared to 16 months with TMZ alone. (12). TTFields show strong effectiveness across different patient groups and tumor types including older patients and those with MGMT promoter unmethylated tumors. This makes it a proven approach to help improve survival outcomes. Patients generally followed TTFs treatment well. The side effects were mostly mild. It was limited to skin irritation, which supports its practicality in clinical practice (12).

TMZ-based chemotherapy continues to be a fundamental part in glioblastoma management. New treatments like TTFields provide a meaningful survival benefit when combined with TMZ. Other therapies such as bevacizumab have not improved overall survival and might negatively affect cognitive function.

Rindopepimut

EGFRvIII is a specific deletion mutation of the epidermal growth factor receptor that is expressed in some glioblastomas. Rindopepimut, a vaccine targeting this mutation, consists of an EGFRvIII-specific peptide conjugated to keyhole limpet hemocyanin (KLH). Single-arm studies of rindopepimut in patients with newly diagnosed, EGFRvIII-positive glioblastoma and minimal residual disease resulted in a median survival of 20-22 months, which was an improvement over the approximately 16 months seen in matched contemporary datasets. The randomized, double-blind, international phase 3 ACT IV trial was conducted to see if rindopepimut, when added to standard chemotherapy, could prolong survival. Patients had undergone maximal surgical resection and had completed standard chemoradiation without progression. Patients were randomized to receive either rindopepimut or a control (KLH) monthly via intradermal injection while concurrently receiving standard temozolomide chemotherapy. Despite the vaccine generating a robust humoral response with a median peak anti-EGFRvIII antibody titer of 1:25,600 in treated patients, the study found no consistent correlation between the speed or robustness of the titer response and clinical outcomes. Additionally, the intensity of tumor EGFRvIII expression did not correlate with outcomes {3}.

Conclusion

Glioblastoma (GBM) is one of the most aggressive and resistant cancers and standard treatments only slightly increase survival. Immune checkpoint inhibitors (ICIs), especially those that target PD-1, PD-L1, PD-L2, and CTLA-4, have shown promise in treating other cancers,but they have not yet produced significant clinical success in GBM. The tumor's low mutational burden,highly immunosuppressive microenvironment physical barriers such as the blood–brain barrier limit the efficacy of ICI monotherapies. Though they haven't always led to higher survival rates, studies using PD-1 inhibitors like nivolumab and CTLA-4 inhibitors like ipilimumab and tremelimumab have demonstrated increased immune activation in particular situations. Also, treatments that target PD-L2 are still in their early stages and require further investigation.

Combination approaches, such as pairing with chemotherapy, radiation therapy or other immune modulators, seem to be necessary for the benefits of ICIs in GBM. Concerns regarding patient safety and treatment tolerance are raised by the possibility that these combinations will raise the risk of toxicity and immune-related side effects.so, it's important to maintain a careful balance between potential benefits and side effects. Improved biomarker identification, treatment timing and arranging optimization like neoadjuvant strategies and overcoming the immune resistant nature of the GBM microenvironment should be the main goals of future research.The efficacy of ICIs may be increased by precision medicine techniques and improved patient selection. Even though immune checkpoint therapy isn't a cure for GBM just yet,it could improve results if used in carefully planned, multimodal treatment plans.

Abbreviations

ICIs – immune checkpoint inhibitors
PD-1 – programmed cell death protein 1
PD-L1- programmed cell death ligand 1
PD-L2 – programmed cell death ligand 2
CTLA-4 - cytotoxic T-lymphocyte-associated protein 4
GBM – glioblastoma multiforme
OS – Overall Survival
PFS – Progression-Free Survival
RCT – Randomized Controlled Trial
TMB- Tumor mutation Burden
ITIM -Immunoreceptor Tyrosine-Based Inhibitory Motif
RRD-HGG -Replication-Repair–Deficient High-Grade Gliomas
KLH - keyhole limpet hemocyanin
TILs - tumor infiltrating lymphocytes

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