REVIEWS

Immune checkpoint inhibitors for the treatment of glioblastoma: Where we are

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ABSTRACT

Despite a history of frequent challenges and roadblocks, there has been recent excitement in the treatment of human cancer, specifically regarding the remarkable efficacy of various immune checkpoint inhibitors including programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) blockers in treating metastatic melanoma, non-small cell lung cancer, and other malignant growths. However, treatment of glioblastoma multiforme (GBM) with immune checkpoint inhibitors so far has not been shown to be as successful in several randomized clinical trials as in other cancer with the exception of one pilot study that found promising results by neoadjuvant administration of Pembrolizimab for the treatment of recurrent GBM. Our article will review the current status of immune checkpoint inhibitors for the treatment of GBM.

Key Words: Glioblastoma, Glioblastoma multiforme, GBM, Immune checkpoint inhibitors, immunotherapy, programmed cell death protein 1 (PD-1), Programmed cell death ligand 1 (PD-L1), cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)

1. INTRODUCTION

Glioblastoma multiforme (GBM) drastically affects the lives of patients who develop the disease, decreasing their quality and quantity of life. Neurological deficits and personality changes are frequently evident in all stages of the disease, associated with compression and infiltration of proximal brain tissue as well as compromised vascularization.[1] Other more non-specific symptoms such as headaches and seizures are also common.

Regardless of circumstance or conditions of manifestation, these symptoms are extremely debilitating towards patient quality of life and are ultimately concrete markers of an underlying tumor leading to fatality. Despite the steps we have taken through surgery, radiotherapy, and chemotherapy in treating the disease, there is a vast unmet patient need for significantly effective GBM therapy, as there still remains no reliable 'cure' for the malignancy that constitutes 15% of CNS tumors.[1]

In current practice, the Stupp protocol has been the standard of care for the patients diagnosed with GBM in the world although Novo-TTF has been approved to be the additional care in the United States based on the positive outcome published by a large randomized trial.[2] This Stupp protocol entails a surgical procedure to confirm and remove tumor tissue mass, followed by concurrent temozolomide (TMZ) and radiotherapy then by adjuvant temozolomide monotherapy.[3] This therapy has yielded a 14.6-month median survival, compared to the average median survival of 12

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months by radiotherapy alone.[3] While the Stupp protocol has brought about a notable improvement in the treatment of GBM over the past decade, it carries a median survival benefit of only 2.5 months.[3] At this point, patients with progression or recurrence of GBM after failure of standard of care are often treated with bevacizumab, which initially blunts tumor progression through inhibition of angiogenesis; however, this loses effectiveness after 5.9 months, and patients subsequently succumb fully to GBM once again.[4] Primary progressive GBM patients need an effective solution to the disease. Recent studies in the field of oncology have shown a dawn in the treatment of metastatic melanoma, non-small cell lung cancer, and many other malignancies with various immune checkpoint inhibitors including PD-1, PD-L1 and CTLA-4 blockers. Treatment of GBM with immune checkpoint inhibitors so far has not been shown to be as successful in several randomized clinical trials as in other cancers. We will review the current status of immune checkpoint inhibitors for the treatment of GBM.

2. Immune checkpoint inhibitors for the treatment of GBM

Unlike conventional prophylactic immune system targeted drugs, which promote the production of antibody responses, cancer immunotherapies are usually designed to generate T-cell responses to malignant cells and growths. Immunotherapeutic approaches for cancer seek to enable the immune system to recognize tumor-associated antigens on tumor cells and to subsequently destroy malignant growths selectively, so as to disrupt as little healthy tissue as possible. Immunotherapy's approach to harness cytotoxic and memory potential of the host immune system has shown great benefit in the treatment of cancer by generating an anti-tumor immune response and blocking some immunosuppression.[5] Recently, checkpoint therapies targeting PD-L1/PD-1 and CTLA-4 pathways have been revolutionary in demonstrating remarkable efficacy in treating other cancers, such as metastatic melanoma[6] and non-small cell lung cancers.[7] These drugs have demonstrated the ability to inhibit the activity of receptor-ligand interactions between tumor cells and T-cells, as well as between T-cells and antigen-presenting cells with great efficacy, yielding significant improvements in patient survival in these cancers.[6] Clinical application of these drugs for GBM is not yet completely understood nor widely practiced, though there is a reason to believe that checkpoint therapies may have much to offer GBM patients. The mechanism of PD1/PD-L1 and CTLA-4 pathways are illustrated in Figure 1.

2.1 PD-1 Inhibiting Drugs: Pembrolizumab and Nivolumab

Currently, Pembrolizumab and Nivolumab are the most commonly used US FDA approved monoclonal PD-1 antibodies for melanoma and non-small cell lung cancer.[7,9] Traditionally, predictive markers in PD-1 antibody therapy are defined by the number of cytotoxic T-lymphocytes inside tumor tissues as well as cancer cell PD-L1 expression level.[10] However, as is the case in GBM, there are no known predictive markers, as the T-lymphocyte infiltration extent and PD-L1 expression level remain particularly elusive, thus shrouding the specific therapeutic benefits of PD-1 antibodies.[11]

Animal studies suggest great efficacy in the usage of PD-1 checkpoint inhibitor drugs when combined with standard TMZ therapy in the treatment of GBM in the GL261 mouse model. Overall survival of the combined group (42 days) was significantly improved compared to control groups with TMZ treatment only (30 days), anti PD-1 treatment only (28 days), and no treatment (25 days). Furthermore, the volume and size of the tumor was significantly decreased in the combined group compared with other groups, and number of CD4 and CD8 infiltrating cells in the tumor was significantly increased in the combined group.[12] Furthermore, preclinical studies support the notion that PD-1 inhibitor is an effective treatment for GBM as a component of a more holistic approach that involves other treatments. Gene-mediated cytotoxic immunotherapy has been proposed as another potential paired therapy, yielding significantly elevated (88%) long-term survival in animal models when combined with PD-1 treatment relative to non-combined controls (0%).[13] Clinical studies involving PD-1 therapy for GBM are relatively limited, with most clinical data involving Pembrolizumab indicating no signal of efficacy for treatment with anti-PD-1 antibodies, despite safety and general patient tolerability.[14] However, a recent clinical study found that compared to adjuvant therapy with PD-1 blockade, neoadjuvant administration of PD-1 blockade before surgery for the treatment of recurrent GBM increased the overall survival (7.5 in control vs 13.7 months in neoadjuvant therapy group, $p = .04$) and progression free survival (2.4 in control vs 3.3 months in neoadjuvant, $p = .03$).[15] The authors theorize that this is most likely due to enhancement of the local and systemic antitumor immune response by tumor cells prior to surgery. This is the first clinical trial that revealed PD-1 monoclonal antibody blockade was associated with statistically significant improvements in overall survival and progression-free survival when administered in the neoadjuvant setting to patients with recurrent GBM.

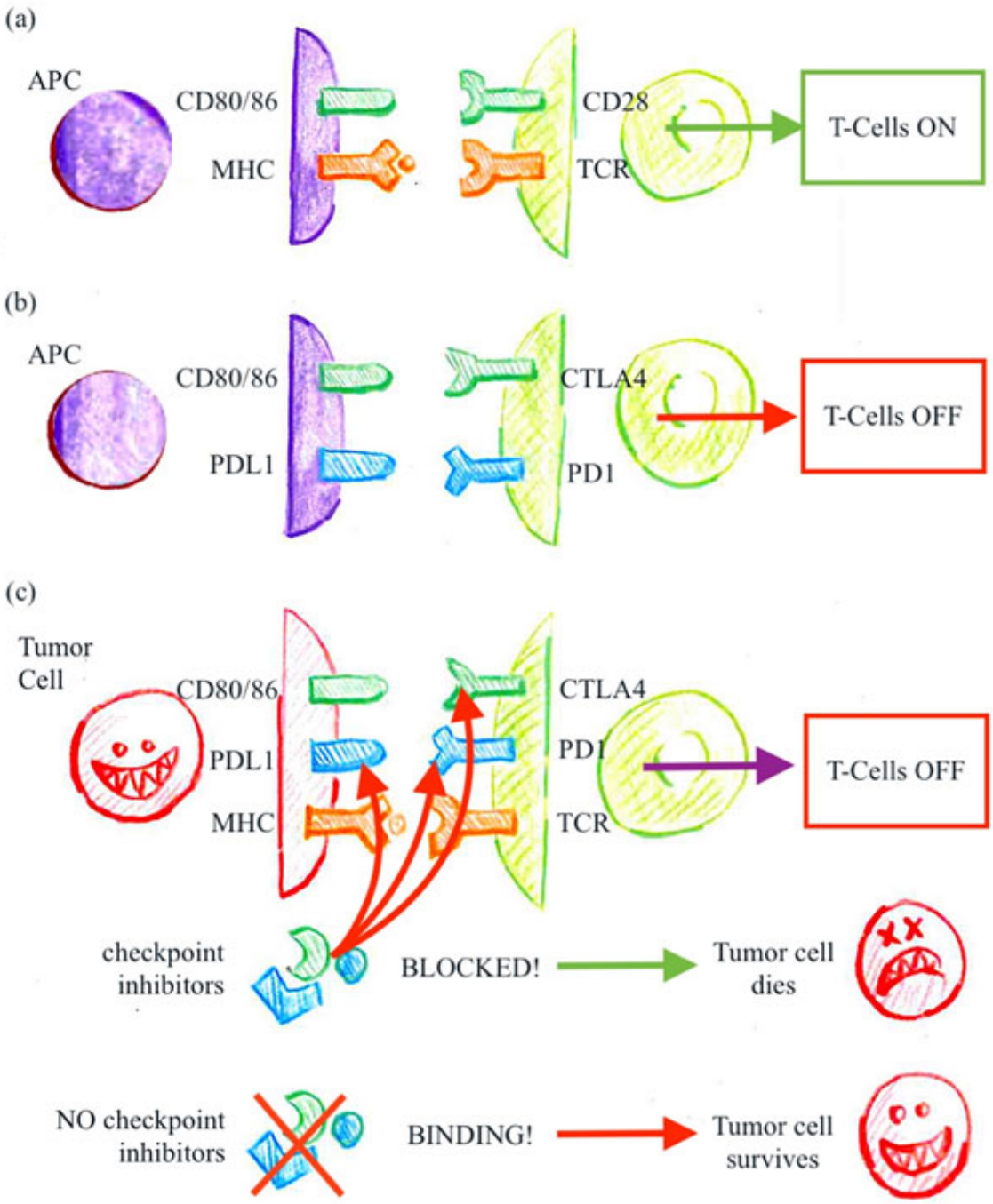

Figure 1. Mechanism of PD1/PD-L1 and CTLA-4 pathways.[8] (a) T-cell activation by antigen presenting cell (APC) requires TCR-MHC interaction as well as a CD28-CD80/86 co-stimulatory checkpoint interaction. MHC molecules are bound to antigen markers that bind TCR to induce T-cell immune signal transduction. (b) PD1 is up-regulated in T-cell membrane following antigen exposure. PDL1 expressed on APC inhibits T-cell activity by binding PD1 in the T cell membrane. CD80/86-CTLA4 interactions inhibit T-cell cytokinesis and activity. APCs suppress T-cell activity via CTLA4-CD80/86 interaction, providing a control signal. Furthermore, interactions between PD1 expressed on T-cells and PDL1 expressed on APCs inhibit T-cell response. (c) The PD1/PDL1 expression is usually highest within the tumor microenvironment. Through a similar mechanism as described in Figure 1(b), the tumor inhibits T-cell immune response. Tumor survives. Immune checkpoint inhibitors selectively block propagation of CTLA4-CD80/86 mediated and PD1/PDL1 mediated checkpoint signals to enhance T-cell immune response. Tumor dies.

2.2 PD-L1 Inhibiting Drugs: Atezolizumab, Aveluma, and Durvalumab

PD-L1 inhibitors operate similarly to PD-1 inhibitors, as they target the same phase of the immune response, albeit a different component of the PD-L1/PD-1 interaction. Current US FDA approved PD-L1 inhibitors include Atezolizumab, Aveluma, and Durvalumab. There is currently a significant gap in the efficacy data of the clinical PD-L1 antibody studies, though animal studies seem to suggest potential therapeutic benefit, reporting that PD-L1 antibody (clone 10F.9G2) increased long term survival in mice/GL261 glioma model (60%, n = 10).[16] The same study found that PD-L1 antibody treatment on mice without T or B cells had no impact on long term survival, implying a mechanism strongly dependent on endogenous immune response. It should be noted that a different study found that concurrent TMZ treatment may actually serve to reduce the efficacy of PD-L1 inhibitors, as TMZ treatment leads to a down-regulation of PD-L1 expression in GBM cells, thus diminishing the target of PD-L1 inhibition.[17] Another study demonstrated administration of PD-L1 antibody combined with CTLA-4 antibody (37% survival) produced greater effects than CTLA-4 antibody alone (20% survival). Furthermore, dual checkpoint inhibition in addition to administration of G47Δ-mIL12 resulted in even more long-term survivors (89% survival) in mice glioma models.[18] Preclinical studies describe PD-L1 antibody therapy to be effective in animal models and to be a potential future direction in GBM therapy, though improvement of PD-1/PD-L1 immunotherapy in GBM is largely reliant on accumulation of clinical data.[19] Others describe significant relationships between high PD-L1 expression, high efficacy with PD-1/PD-L1 inhibition, and high patient mortality rate, potentially warranting these treatments for brain gliomas in clinical cases.[20] One ongoing clinical study has revealed that anti-PD-L1 monotherapy Durvalumab appears to be well tolerated in patients and shows significantly durable activity in a subset of Bevacizumab-naive recurrent GBM patients.[21] Another clinical study noted the safety and tolerability of Atezolizumab as well as some therapeutic effect in select patients, recommending further anti-PD-L1 combination studies for GBM.[22]

2.3 CTLA-4 Inhibiting Drugs: Ipilimumab and Tremelimumab

Cytotoxic T-lymphocyte antigen-4 blockade (CTLA-4) drugs act on the CTLA-4 receptor expressed on glioma T-regs and T-cells. CTLA-4 is a strong immunosuppressive antigen, blockage of which inhibits the negative signal that inhibits T-cell activation, expansion, and activity.[23] Current US FDA approved CTLA-4 inhibiting drugs include Ipilimumab and Tremelimumab. Preclinical results testing a combined CTLA-4, PD-L1, and IDO targeted therapy demonstrated strong evidence for efficacy, yielding a 78% survival rate in treated GBM mice and a 100% mortality rate in non-treated GBM mice.[16] These results have triggered clinical studies on the effects of CTLA-4 blockade on GBM. For example, Ipilimumab and Bevacizumab in combination showed promising therapeutic benefit with a manageable toxicity profile and some degree of efficacy.[10] Research in this area only began in the last few years. More clinical trials are ongoing.

3. Some toxicities of immune checkpoint inhibitors

By their very nature, CTLA-4 and PD-1/PD-L1 expression strikes a balance between self-tolerance and autoimmunity.[24] Although toxicity with CTLA-4 and PD-1/PDL-1 antibodies is not lethal, it is common for patients to experience a number of immune related side effects affecting primarily skin, gastrointestinal, renal, and endocrine systems (see Table 1). It was also found that 60% of ipilimumab-treated patients experience such symptoms, specifically rash, colitis, neuropathy, and nephritis.[25] Furthermore 10-15% of patients will eventually develop more serious symptoms, including hypophysitis, hepatitis, inflammatory colitis, epidermal necrolysis, fatal colitis, and pneumonitis. It should be noted that the onset of these symptoms ranges on the scale of weeks to months, whereas chemotherapy symptoms are much more rapid, occurring within hours to days.[25] Another study evaluating the safety of combined effects of Tremelimumab and Durvalumab found similar results, with 80% of patients experiencing adverse side effects in the form of diarrhea, fatigue, pruritus, colitis, or increased lipase.[26] While some of these side effects can be life threatening, as is the case with inflammatory colitis, oftentimes some toxicities are also known to be asymptomatic laboratory abnormalities of unclear significance, most of which resolve without apparent sequelae. The usage of these medicines for the treatment of GBM is still being closely monitored in various clinical studies in order to best assess the risk/benefit ratios and to better understand dose-limiting toxicities, adverse effects, safety, and tolerance.[25] It would be optimal for patients to receive constant monitoring, which may entail regular clinical and pharmacokinetic assessments to prevent occurrence of and deterioration from toxicity of checkpoint inhibitors. In the case of metastatic melanoma, toxicity profile is measured with MRI or CT scan with contrast, which may be applied to GBM with similar treatment.[11]

Table 1. Adverse effects of any grade from immune checkpoint inhibitors

	PD-1	PD-L1	CTLA-4	Durvalumab & Tremelimumab	Nivolumab & Ipilimumab
Common (≥ 10%)	Fatigue, Diarrhea Rash, Pruritus, Asthenia, Nausea Hypothyroidism [9]	Fatigue, Malaise, Diarrhea, Headache, Nausea, Asthenia[22]	Pruritus, Diarrhea, Fatigue, Rash[9]	Diarrhea，Pruritus Rash，Amylase increase [26]	Diarrhea, Fatigue, Pruritis, Rash, Nausea, Vomiting, Decreased appetite, Pyrexia, Colitis, Headache, Arthralgia, Dyspnea, Increased lipase, Hypothyroidism, Hyperthyroidim, AST elevation, ALT elevation[6]
Uncommon (< 10%, ≥ 1%)	Arthralgia, Vitiligo Hyperthyroidism, Colitis, Hepatitis[9]	AST increase, ALT increase, Apraxia, Arthralgia, Back pain, Low appetite, Vomiting, Dermatitis, Dry mouth[22]	Asthenia, Nausea Colitis, Arthralgia, Vitiligo, Hypophysitis Hyperthyroidism Hypothyroidism[9]	Colitis, Hypothyroidis, Increased lipase, AST increase, ALT increase, TSH decrease, TSH increase, Creatinine increase[26]	Abdominal pain, Vitiligo, Increased amylase level, Decreased weight, Cough, Pneumonitis[6]
Rare (< 1%)	Hypophysitis, Type I diabetes mellitus, Uveitis[9]		Nephritis, Myositis, Pneumonitis[9]		

Note. AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase

4. DISCUSSION

Immune checkpoint inhibitors have demonstrated a wide scope of applicability and efficacy across non-small cell lung cancer, metastatic melanoma, and other malignancies in recent years,[27] sparking a justified and necessary curiosity in their application in GBM. The current clinical paradigm of GBM patients leaves much to be desired; long-term treatment progress has been modest in these past few decades, and GBM mortality rate has remained consistently troubling.[1] A number of studies point towards the potential efficacy and safety of the checkpoint inhibition model of GBM treatment, though the few clinical trials that have been performed call for much further investigation. These drugs are relatively new, and many are still currently being tested both as single agents and in combination with other more common treatments for GBM.[11] So far, animal models and preclinical studies have yielded promising results in efficacy, specificity, and toxicity when compared with controls undergoing conventional anticancer therapies. Furthermore, the high expression of PD-L1 in GBM makes it a particularly convenient candidate target for further clinical research.[28] The research paradigm surrounding the application of checkpoint inhibition for GBM is an optimistic one: many animal model studies report significantly increased survival rates, and preclinical studies describe manageable toxicity and potential for efficacy. Despite the notable strides forward in immunotherapy as a whole and seemingly promising results in preclinical studies, clinical data have not yet yielded significant improvements in GBM therapy, as most studies reported significant effects in only a select few individuals.[17–20] This dissonance indicates potential deficiencies in clinical models, as the differing immune systems of mice and humans may distort reliable predictability between preclinical and clinical results. This issue could be partially resolved by means of better animal models or by further advancing personalized drug-screening and treatment options for GBM patients. It is suggested that cancer checkpoint inhibition therapies be considered in the context of combination management to maximize therapeutic benefit.[10,11] Patients undergoing single-agent or combinatorial checkpoint therapy for GBM should be under evaluation for immune regulation, undergo constant monitoring, and be treated with pharmacological intervention accordingly to further ensure patient benefit and safety.[11] Symptoms related to treatment are also worth mentioning. Immune response assessment is still particularly difficult in GBM cases, and checkpoint inhibition treatment can lead to a variety of negative symptoms. Thus, it is important to evaluate immune responses to tumor and normal tissue throughout treatment application in order to achieve the optimal anti-cancer immunity while maintaining

immunologic tolerance to self-antigens to avoid an autoimmune response.[24] Furthermore, it is necessary to account for potential variables and local inflammation so as to effectively maximize therapeutic benefit.[11] With careful attention to individual patient response to treatment and further assessment of the clinical value of immunotherapy in GBM, checkpoint inhibition may reveal itself to be a valuable method in the treatment of GBM.

5. Conclusion

The recent advances in checkpoint immunotherapy in other cancers have potentially significant implications in the treatment of GBM. By targeting various biomarkers in the PD-1/PD-L1 and CTLA-4 pathways, immune checkpoint inhibitors may still be an important future oncological tool for GBM. Pre-clinical and animal studies have produced particularly promising results demonstrating the apparent efficacy of checkpoint inhibition in GBM, especially in combination with other therapies. However, clinical trials involving these drugs have not produced consistent significant therapeutic responses in patients,[29] with the exception of one pilot study that found promising results by neoadjuvant administration of Pembrolizimab for the treatment of recurrent GBM.[15] The treatment of GBM with immune checkpoint inhibitors is still a relatively new practice, which will continue to be shaped, understood, and refined by additional clinical application and will one day provide hope and healing to GBM patients.

Conflicts of Interest Disclosure

The authors declare no conflict of interest

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