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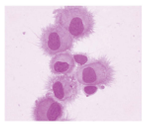

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REVIEW

PD-1/PD-L1 immune checkpoint inhibitors in glioblastoma: clinical studies, challenges and potential

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ABSTRACT

Immune checkpoint inhibitors (CIs) have changed the landscape of tumor immunotherapy. Glioblastoma (GBM) remains the most common primary malignant brain tumor in adults and has a very poor prognosis. Due to the high invasiveness and aggressiveness of GBM, there is considerable interest in programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) treatment. However, the immunosuppressive and immune-privileged characteristics of GBM limit the efficacy of CIs. While clinical studies of CI monotherapies have shown unsatisfactory survival benefits, new treatment strategies have received attention. Multiple clinical studies have focused on combination of standard therapy (temozolomide, radiotherapy), targeted therapy and other immunotherapies, and some have reported results. Here, we reviewed recent clinical trials of anti-PD-1/PD-L1 monotherapy, studies with neoadjuvant strategies, and preclinical and clinical studies of combination immunotherapies for GBM. The preliminary clinical reports in certain subsets of patients with hypermutated or mismatch repair system deficiency GBM are also discussed.

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Introduction

Glioblastoma (GBM) is the most common primary brain tumor in adults and exhibits high aggressiveness, with a median overall survival (OS) time of less than 2 years and a 5-year OS rate of less than 10%[1]. GBM represents one of the greatest therapeutic challenges of the modern era, with a low cure rate, high recurrence rate, and limited survival time. Therapeutic options are extremely limited at both the time of new diagnosis and relapse.

Studies on GBM therapies have been performed, and immune checkpoint inhibitors (CIs) have received considerable attention. CIs activate the anti-tumor response by inhibiting negative immune regulatory pathways, providing new therapeutic approaches for GBM.[2] The main category of CIs is monoclonal antibodies that target the programmed cell death protein-1 (PD-1) or its ligand (PD-L1); this category includes pembrolizumab, nivolumab, durvalumab, and atezolizumab. These anti-PD-1/PD-L1 CIs have shown significant efficacy for some tumors (such as melanoma,[3-5] non-small cell lung cancer (NSCLC),[6,7] and small cell lung cancer (SCLC)[8]) in clinical trials and have been approved for multiple tumors. For GBM, although preclinical studies have shown some potential for treatment, anti-PD-1/PD-L1 monotherapy has shown few satisfactory results in clinical studies. Most trials revealed a low tumor response, and the treatment did not prolong patient survival, which limited its therapeutic application. We summarized the existing clinical studies of anti-PD-1/PD-L1 antibodies and explored the directions for CI treatment, including the treatment of specific hypermutated tumors, neoadjuvant therapy, and combination therapies, to investigate the potential of anti-PD-1/PD-L1 treatment for GBM.

Anti-PD-1/PD-L1 monotherapy

Most clinical studies of GBM anti-PD-1/PD-L1 monotherapy have shown limited efficacy. Table 1 showed identified clinical trials of anti PD-1/PD-L1 monotherapies. Pembrolizumab, which is FDA approved for NSCLC, melanoma, hepatocellular carcinoma and several other cancers, did not prolong the survival of patients with GBM when used as a single agent. The Keynote-028[9] clinical trial investigated pembrolizumab monotherapy in 26 patients with recurrent GBM, and reported limited survival benefits: median stable disease (SD) of 39.4 weeks (7.1–85.9 weeks), median progression free survival (PFS) of 2.8 months (1.9–9.1 months), and median OS of 14.4 months (10.3-not reached). Several studies of high grade gliomas (WHO grade 3 and 4) also showed that pembrolizumab monotherapy has limited efficacy compared with control groups.[10,11] Nivolumab is another approved, widely used CI. Checkmate 143, the first large-scale phase 3 clinical trial involving CI treatment of GBM, initially evaluated ipilimumab + nivolumab. However, the major results were regarding nivolumab monotherapy due to increased adverse effects with ipilimumab.[12] Compared with the bevacizumab-treated control group, nivolumab did not significantly improve survival; the 12-month OS was 42% in both arms, while the median OS was 9.8 months in the nivolumab group and 10.0 months in the bevacizumab group; the median PFS was 1.5 months and 3.5 months in the nivolumab and bevacizumab groups,

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Table 1. Clinical trials investigating PD-1/PD-L1 immune checkpoint blockade with glioblastoma.

Dates	2018.11–2020.12	2017.3–2020.3	2016.11–2019.11	2017.11–2020.2	2018.6–2020.2	2018.11–2021.11	2018.9–2021.6	2019.3–2024.2	2018.10–2023.10	2019.3–2034.12	2019.2–2022.4	2019.1–2020.4	
Population	30	30	6	34	30	94	20	30	30	7	180	20	
Outcome Measures	PFS, OS, Toxicity, TTP, OR	Toxicity	PFS, OS	OS, PFS, PFS-6, PFS-12, PFS-24, Tumor Response	PFS, OS, DLT, ORR	OS, PFS, PFS-6, ORR	Proportion of Patients That Have Interferon Gamma Level Rise	PFS, OS, Toxicity	Toxicity, Personalized Neoantigen Peptide Vaccine Generation	OS, PFS, Toxicity, ORR	OS, PFS, ORR, Toxicity, DOR	OS, PFS, Toxicity, ORR, DCR, Immunogenicity	
Design	Single Group Assignment	Single Group Assignment	Single Group	Randomized Parallel Assignment	Single Group	Non-Randomized Parallel Assignment	Single Group	Non-Randomized Parallel Assignment	Non-Randomized Sequential Assignment	Single Group	Single Group Assignment	Sequential Assignment	
Status	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	
Phase	1/2	2	1	1/2	1	2	1	1	1	1	2	1	
Combination	VXM01 (Anti-VEGF2)			Laser Interstitial Thermotherapy	Laser Interstitial Thermotherapy	RT, Bevacizumab		MK-4166 (Anti-GITR) INCB024360 (IDO1 Inhibitor)	Neovax	Egfrviii-CAR-T	Lenvatinib	TTAC-0001 (Anti-VEGF2)	
Target	PD-L1	PD-L1	PD-1 CTLA-4	PD-1	PD-L1	PD-1	PD-1 LAG-3	PD-1 CTLA-4	PD-1 CTLA-4	PD-1	PD-1	PD-1	
Checkpoint Inhibitor	Avelumab	Avelumab	Nivolumab Ipilimumab	Pembrolizumab	Avelumab	Nivolumab	Nivolumab BMS-986016	Nivolumab Ipilimumab	Nivolumab Ipilimumab	Pembrolizumab	Pembrolizumab	pembrolizumab	
NCT number	NCT03750071	NCT03047473	NCT03233152	NCT03277638	NCT03341806	NCT03743662	NCT03493932	NCT03707457	NCT03422094	NCT03726515	NCT03797326	NCT03722342	
Dates	2019.8–2022.1	2019.10–2023.10	2019.5–2023.12	2019.8–2023.6	2019.9–2021.12	2019.9–2023.6	2015.1–2018.12	2015.6–2017.3	2017.3–2019.1	2016.9–2020.6	2017.3–2020.8	2018.5–2021.1	2014.11–2021.8
Population	60	30	56	15	51	30	175	29	52	36	43	52	46
Outcome Measures	OS, OS-9, PFS, T Cell Levels, Cytokine Levels, Tumor Response, Toxicity	Toxicity, Personalized Neoantigen Peptide Vaccine Generation, Candidate Tumorspecific Neoantigen Indentification	OS-12, ORR, PFS, PFS-6, PFS-12, TTF, Quality of Life, PD-1/PD-L1 Expression	OS, PFS, Toxicity, ORR	PFS, Toxicity	OS, PFS-6, Toxicity, ORR, RR, MDR	ORR, OS-12	RR, PD-L1 Expression, Toxicity	OS, PFS-6, ORR,				
		Neurocognitive Function	T-Cell Changes in Blood, MRI, Toxicity, OS, PFS	Toxicity, PFS-6, PFS, OS, ORR, MDR	Toxicity, OS-18, Molecular Changes	Toxicity, PFS-8, T Cell Response							
Design	Randomized Parallel Assignment	Non-Randomized Sequential Assignment	Single Group	Single Group	Non-Randomized Parallel Assignment	Non-Randomized Parallel Assignment	Single Group Assignment	Single Group Assignment	Parallel Assignment	Randomized Parallel Assignment	Single Group	Non-Randomized Parallel Assignment	
Randomized Parallel Assignment													
Status	Not Yet Recruiting	Not Yet Recruiting	Not Yet Recruiting	Not Yet Recruiting	Not Yet Recruiting	Not Yet Recruiting	Completed	Completed	Completed	Active, not Recruiting	Active, not Recruiting	Active, not Recruiting	Active, not Recruiting
Phase	1	1	2	1	2	1	1/2	2	2	2	2	1/2	1
Combination	Il13ralpha2-CAR-T	Personalized Neoantigen Vaccine		Mbg453 (Anti-TIM3) RT	Survaxm Sargramostim	Bms-986205 RT TMZ	Varlilumab		Axitinib		Hypofractionated Radiation Therapy	Ino-5401 Ino-9012 RT TMZ	RT Personalized Neoantigen Vaccine
Target	PD-1 CTLA-4	PD-1 CTLA-4	PD-1	PD-1	PD-1	PD-1	PD-1	PD-1	PD-L1	PD-L1 CTLA-4	PD-L1	PD-1	PD-1
Checkpoint Inhibitor	Nivolumab Ipilimumab	Nivolumab Ipilimumab	Pembrolizumab	Spartalizumab	Pembrolizumab	Nivolumab	Nivolumab	Nivolumab	Avelumab	Durvalumab Tremelimumab	Avelumab	Cemiplimab	Pembrolizumab
NCT Number	NCT04003649	NCT04015700	NCT03899857	NCT03961971	NCT04013672	NCT04047706	NCT02335918	NCT02550249	NCT03291314	NCT02794883	NCT02968940	NCT03491683	NCT02287428

Clinical trials were identified on the clinicaltrials.gov website as of November 2019.The search terms were as follows: 'glioblastoma', 'GBM', 'glioma', 'brain tumor', 'immune checkpoint inhibitor', 'immune checkpoint blockade', 'PD-1', 'PD-L1', 'pembrolizumab', 'nivolumab', 'durvalumab', and 'atezolizumab'.

PD-1: programmed cell death 1, PD-L1: programmed cell death-ligand 1, CTLA-4: cytotoxic T-lymphocyte-associated protein 4, LAG-3: lymphocyte activation gene 3, VEGF: vascular endothelial growth factor, IDO1: indoleamine 2,3-dioxygenase 1, GITR: glucocorticoid – induced tumor necrosis factor receptor, EGFR: epidermal growth factor receptor, RT: radiotherapy, TMZ: temozolomide, CAR-T: chimeric antigen receptor T-cell immunotherapy, OS: overall survival, PFS: progression-free survival, OS-12: 12 month overall survival rate, OS-18: 18 month overall survival rate, OS-9: 9 month overall survival rate, PFS-6: 6 month progression-free survival rate, PFS-8: 8 month progression-free survival rate, PFS-12: 12 month progression-free survival rate, ORR: objective response rate, RR: radiographic response rates, DOR: duration of response, MDR: median duration of response, TTF: time to treatment failure, MRI: magnetic resonance imaging, DLT: dose-limiting toxicity, DCR: disease control rate

respectively. The anti-PD-L1 antibodies[13] atezolizumab[8] and durvalumab[14] have been approved for several cancers. A phase 1 clinical trial of atezolizumab monotherapy involving 16 patients with recurrent GBM[15] demonstrated unextended survival, except for 3 patients with IDH or POLE mutations who survived longer than 16 months. A phase 2 trial[16,17] evaluating durvalumab in 5 GBM cohorts published preliminary results. Data from subgroups indicated partially clinical benefits. In the arm involving 30 patients with recurrent GBM who received durvalumab monotherapy, the overall disease control rate was 60.0% (4 with a partial response, 14 with SD), the median OS was 28.9 weeks (22.9-not reached), and the median PFS was 13.9 weeks (8.1–24.0 weeks). In conclusion, the efficacy of CI monotherapy in treating GBM is not satisfactory. It is necessary to further analyze the underlying reasons and develop new treatment strategies.

The efficacy of CIs may be affected by several factors, including tumor cell PD-L1 expression,[18] tumor-infiltrating lymphocytes (TILs),[19] tumor-infiltrating myeloid cells (TIMs),[20] tumor mutation burden (TMB), new antigen burden, microsatellite instability (MSI), mismatch repair (MMR) system status, and POLE mutation status.[21] As high PD-1 expression may be correlated with a worse prognosis in patients with GBM,[22] the results that 88% of patients with newly diagnosed GBM and 72.2% of patients with recurrent GBM have high PD-1 expression[18] may be a challenge for further studies. In addition, since the existence of TILs is the basis of its effectiveness, the 'cold' microenvironment and the depletion of TILs in GBM also causes challenges for efficacy.[19]

Patients with specific GBM subtypes may benefit more from CI therapies. A higher TMB, higher MSI, neoantigen, MMR system deficiency (MMRD), and germline POLE mutation usually suggest better efficacy, which has been confirmed in clinical practice.[23-26] In patients with melanoma,[27] NSCLC,[28] colorectal cancer,[29] and several other tumors,[30] hypermutated subtypes are often associated with better CI efficacy. In one case report about a GBM patient with hypermutation and POLE germline mutation,[23] radiographic response and increased lymphocyte infiltration were observed, suggesting preliminary effectiveness. However, the definition and classification of hypermutation are inconclusive. The determination of hypermutation is mainly based on TMB, which quantitatively reflects the quantity of tumor mutations. Different thresholds have been reported for pan-cancer analysis, and there is no consensus yet for the critical definition of 'hypermutation'.[31,32] For GBM, several different important criteria were used in published studies. Hodges et al. used TMB> 20 mutations/1.4 Mb as the criterion for glioma hypermutation.[33] Johnson et al. chose TMB> 20 mutations/Mb in pediatric brain gliomas.[34] Campbell et al. classified tumors with TMB> 9 mutations/Mb as hypermutated and tumors with TMB> 100 mutations/Mb as ultra-high mutated in GBM.[24,31] Bouffet et al. defined hypermutation as >100 mutations per exome in GBM.[26] In follow-up studies, the appropriate definition of 'hyper' should be further classified and unified.

Another type of GBM associated with better CI efficacy is MMRD. The four MMR genes (PMS2, MLH1, MSH2, and MSH6) are responsible for correcting DNA mismatches during replication, maintaining DNA stability.[25] MMRD GBM demonstrated high TMB and predicted high neoantigen load, even higher than those of melanoma, lung cancer, and colon cancer, which are usually considered 'immuno-responsive' tumors.[26] In an MMRD pedigree study,[26] 2 pediatric siblings received nivolumab after GBM recurrence (newly diagnosed at 3.5 years and 6.5 years and recurrent at 4 and 7 years, respectively), resulting in a significant radiologic and clinical response. Follow-up MRI showed tumor disappearance, which was stably maintained for a long time. An abstract[35] from the 2019 American Society of Clinical Oncology (ASCO) conference also reported that after treating 12 high grade glioma patients (with weak and absent MMR expression, according to immunochemistry) with pembrolizumab, 4 patients developed SD. In the weak MMR and absent MMR subgroups, the median OS was 2.8 months and 5.6 months, respectively, and the PFS was 1.8 months and 3.1 months, respectively. Although the tumors progressed in all patients, survival data showed that patients without MMR might benefit from pembrolizumab monotherapy.

Neoadjuvant therapy

As a new dosing regimen for current CI monotherapy, neoadjuvant treatment has been reported to reverse the immunosuppressive properties of the GBM microenvironment, enhance local and systemic antitumor immune responses, improve chemokine expression, and increase immune cell infiltration in tumors.[36] A single-arm phase 2 clinical trial treated 30 patients with GBM (27 recurrent and 3 newly diagnosed) with neoadjuvant nivolumab[37] and found a median OS of 7.3 months, and a median PFS of 4.1 months. Furthermore, 2 patients had PFS of 28.5 and 33.3 months. Multiple molecular and cellular analyzes showed that after neoadjuvant therapy, the expression of chemokines in tumor tissues was enhanced, and immune cell infiltration was increased. Another randomized trial involving 35 patients with recurrent GBM[38]showed that survival was longer in the neoadjuvant pembrolizumab group than adjuvant pembrolizumab group (median PFS of 2.4 months and 3.3 months, respectively, and median OS of 13.7 months and 7.5 months, respectively). Tumor gene expression profiles also converted in the experimental group, with enhanced interferon-γ-related gene expression, increased T cell clonality, and downregulated PD-1 signal. These two clinical trials suggest therapeutic potential for neoadjuvant therapy. Furthermore, a retrospective study investigated 66 CI-treated patients with recurrent GBM to specifically identify molecular changes caused by neoadjuvant therapy and to predict its efficacy.[39] In responders, the expression of mitogen-activated protein kinase (MAPK) pathway-related genes (PTPN1, BRAF) increased, accompanied by an increase in T cell clone diversity and tumor microenvironment heterogeneity. However, in non-responders, enriched PTEN mutations indicated an immunosuppressive microenvironment, together with a failure of selective recruitment of lymphocytes. Such molecular

alterations may act as response predictors and should be considered in further clinical investigations of neoadjuvant CI therapy.

Preclinical studies of combination therapy

As the efficacy of CI monotherapy has not meet expectations, combination therapies with CIs and other treatments are being pursued. Preclinical animal studies have indicated partial potential of the combination of standard therapy, targeted therapy, or other immunotherapies.

Addition of the standard medication temozolomide (TMZ) may enhance antitumor efficacy in rodent models.[40,41] Local TMZ can increase the number of CD3 + T cells in the peripheral blood. Local TMZ + anti-PD1 treatment produced longer survival and higher circulating lymphocyte numbers than in monotherapy.[40] However, systemic TMZ chemotherapy may result in lymphodepletion, abrogate part of the immune response induced by CIs, and decrease immune memories,[42-44] suggesting that TMZ administration strategies should be considered.[45] For radiotherapy (RT) rodents treatedwith anti-PD1combined with RT had a longer survival time with increased TILs and decreased local immunosuppression, indicating therapeutic potential.[46]

The targeted monoclonal antibody bevacizumab has been regularly used in recurrent GBM as salvage therapy since it was FDA approved in 2009.[47,48] PD-L1 expression is upregulated in bevacizumab refractory tumors, and CIs may restore sensitivity to bevacizumab.[50] Bevacizumab can also promote the efficacy of CIs by inducing local high endothelial venules (HEVs),[50] regulating the immune microenvironment, and promoting the antitumor immune response.[50] However, the specific effects of GBM treatment still need to be further explored.

Combinations with other immunotherapies are also considerable strategies. TIM-3 and LAG-3 are co-inhibitory receptors expressed in TILs and can lead to immune exhaustion in the GBM microenvironment.[51,52] The combination of anti-TIM3 + anti-PD1 + focal radiation and anti-LAG3 + anti-PD1 resulted in prolonged survival in murine gliomas,[53,54] and follow-up examinations also revealed immune cell infiltration and immune memory cell formation. The combined measles virus (MV) + anti-PD-1-treated mouse group showed an extended survival time with an increased number of TILs.[55] The combination of dendritic cell (DC) vaccines + anti-PD1 extended survival time and increased integrin homing and immunologic memory markers on TILs,[56] which indicated a potential for clinical translation.

Pre-clinical research, especially the integration of preclinical models, may assist in optimizing combination strategies and match them with appropriate patient subsets.[57] However, the translation of preclinical murine models into clinical studies is an inevitable challenge.

Clinical studies of combination therapy

Clinical studies have provided valuable information about combination therapies. Table 1 also includes essential information from combinational clinical trials. The phase 3 clinical trial Checkmate 498[58] focused on newly diagnosed, MGMT unmethylated GBM. Preliminary published results showed that compared to TMZ + RT therapy (without TMZ), nivolumab + RT treatment did not meet the main endpoint of prolonged OS. The phase 2 trial Checkmate 548[59] focused on newly diagnosed, MGMT methylated GBM and reported that compared to TMZ + RT treatment, the PFS of patients treated with nivolumab + TMZ + RT was not extended, and the OS has not been reported. At the 2019 ASCO conference, optimistic data were released. Patients with newly diagnosed MGMT unmethylated GBM were treated with durvalumab + RT after surgery followed by durvalumab monotherapy. Among 40 patients, the median OS was 15.1 months (12.0–18.4 months), and 8 (20%) patients remained alive when the abstract was published, with ongoing survival ranging from 15.7 to 34.9 months.[60] Initial trials did not demonstrate significantly improved efficacy after combination with standard therapy, and further studies have been pursued. On the other hand, due to optimistic data reported from small-scale studies, and several ongoing clinical trials, the combination with standard therapy should not be totally negated. The failure of combination studies to date should not detract from future attempts, but that the ideal drug pairings and patient population require careful consideration.

Several clinical trials of bevacizumab combination therapy have published preliminary results. A phase 2 clinical trial involving bevacizumab naïve patients with recurrent GBM reported primary data at the 2018 ASCO conference: compared with pembrolizumab monotherapy, combination with bevacizumab did not show superiority with regard to survival time (median OS of 10.3 months vs 8.8 months, 6-month PFS of 6.7% vs 26%).[61] Two phase 2 trials reported that the combination of pembrolizumab and bevacizumab could benefit tumor control and prolong survival time.[62,63] Another phase 2 clinical trial treated bevacizumab refractory recurrent GBM with durvalumab + continuing bevacizumab.[64] Eight patients (36%) exhibited an OS ≥22 weeks, and 11 patients (50%) had a PFS ≥8 weeks. The results suggested that durvalumab + bevacizumab exhibited preliminary activity. The results of these studies indicate that bevacizumab combination therapy may be effective, and further investigations are warranted.

The results of clinical studies in combination with other immunotherapies are limited, but multiple clinical trials are in progress (shown in Table 1). Nivolumab + ipilimumab combination treatment for melanoma showed improved PFS compared with monotherapy,[65] but due to differences in tumor conditions, the efficacy of this combination for GBM is limited by safety and tolerability. In the Checkmate 143 trial, in the nivolumab + ipilimumab group, 40% of patients were forced to discontinue treatment due to intolerance.[66] Several trials of combinations with vaccines, oncolytic viruses, and CAR-T therapies are in progress, and further results are anticipated.

Safety and tolerability

PD-1 inhibitors are generally well tolerated.[67,68] According to the National Comprehensive Cancer Network (NCCN)[69,70] and European Society for Medical Oncology (ESMO)[71] guidelines, the overall incidence of adverse events (AEs) caused by PD-1 antibodies was 26.8%, the incidence of high-level AEs

was 6.1%, and no significant differences in AEs were observed between the PD-1 and PD-L1 antibody groups.[72]The Checkmate 143[66] trial showed that the most common AEs associated with nivolumab included fatigue, diarrhea, headache, elevated lipase, and nausea. Patients had a greater tolerance for nivolumab than ipilimumab, and the incidence of AEs increased with the ipilimumab dosage. For neurological AEs, the overall incidence was 6.1%,[72] with a highly heterogeneous clinical spectrum. The most commonly reported AEs were grade 1–2, included headaches, encephalopathies and meningitis.[72] In Checkmate 143, headaches and seizures occurred most frequently among neurological AEs, which were also well tolerated.[73] There was also brain specific CI-related pseudo-progression reported. Pseudo-progression is due to a locally stimulated immune response, which can mimic the radiologic features of progression including enhancement and edema.[74] Therefore, imaging features of tumor deterioration at the initial stage of immunotherapy cannot exclude subsequent clinical benefit according to the Immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria.[75] In clinical practice, it is necessary to correctly distinguish pseudo-progression from true progression and determine treatment failure.

CI-related AEs need to be discovered in a timely manner and closely monitored. With prompt intervention, most can be effectively managed.[76] Glucocorticoids can reverse nearly all immune-related AEs and are suggested for grade 3–4 or prolonged grade 2 AEs.[77] Prolonged use of glucocorticoids may have benefits in preventing the recurrence of AEs, especially pneumonia and hepatitis. Glucocorticoids are widely used in GBM patients to reduce tumor-related cerebral edema and radiation necrosis.[78,79] Nonetheless, the impact of glucocorticoids on patients with GBM treated with CIs has not been fully investigated. Evidence has shown that glucocorticoids do not reduce the efficacy of immunotherapy, but pre-administration before treatment may be associated with immunosuppression.[80,81] The impact of glucocorticoids on OS also remains conflicting.[66,79,82] Thus, in clinical practice with patients with GBM, the clinical beneficial effect, immune suppressing effect, CI-related AEs reversing effect, and survival effect of steroids must be balanced. Additionally, oral mycophenolate, intravenous infliximab (anti-TNFa mAb), plasma exchange, and infusion of anti-thymocyte immunoglobulin can be considered for severe AEs.[69] Resuming immunotherapy after severe AEs requires cautiousness, and follow-up monitoring is necessary.[76]

Conclusion

At present, the use of anti-PD-1/PD-L1 CIs for GBM has received attention, but the overall efficacy is still unsatisfactory. Due to the unique properties of GBM, many challenges still need to be overcome before reaching a 'breakthrough'. Some studies have supported that screening specific patient subgroups may result in the possibility of greater benefits. Neoadjuvant administration, as a new treatment strategy, needs more clinical studies to assess its safety and efficacy. Data from large-scale clinical trials focusing on CIs combination therapies are limited, and most of the published results were negative, demonstrating no significant survival benefits. However, some small-scale studies and subgroups from large-scale studies reported varying degrees of benefits, indicating that detracting certain combination strategies still needs consideration. Furthermore, multiple clinical trials are under investigation, and the results are highly anticipated. Further studies surmounting challenges, such as investigating immunotherapy endpoints, identifying biomarkers for personalized treatment, and developing useful imagination evaluation criteria, are still being pursued.[57] In conclusion, CIs for GBM have multiple challenges and potential, and more in-depth studies and clinical trials are needed.

Disclosure of Potential Conflicts of Interest

The authors declare that there is no conflict of interest. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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