The Efficacy and Safety of PD-1/PD-L1 Checkpoint Blockade Immunotherapy in Recurrence Glioblastoma: A Meta-Analysis

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Abstract

Purpose: The efficacy of PD-1/PD-L1 checkpoint blockade immunotherapy in recurrence glioblastoma remains unclear. The aim of this meta-analysis is to access the survival outcomes of immunotherapy in these patients.

Methods: A comprehensive electronic literature search of PubMed, Web of Science, Embase and Cochrane Library was conducted up to August 22, 2021. The main evaluation data were the overall survival (OS) rate at 12 months and the progression-free survival (PFS) rate at 6 months. The secondary evaluation data was the incidence of serious adverse events(grade 3 or greater AEs). The study was performed using R“meta” package.

Results: Seven studies met the inclusion criteria, which totally contained 343 participants. The 12-month OS in recurrent GBM were 40% (95% CI: 89.2% -95.1%), while the 6-month PFS 16.0% (95%CI 9%–23%). The overall incidence of adverse reactions is approximately 25% [0.13; 0.40], the toxicity of immunotherapy was acceptable.

Conclusions: Compared with survival data for BEV (bevacizumab) /BPC(best physician's choice chemotherapy) treatment, immunotherapy seemed to improve overall survival and progression-free survival, Meanwhile, the toxicity of immunotherapy was tolerable. Further randomised controlled clinical studies are needed to confirm these findings. And also suggests that the earlier we apply anti-PD-1/PDL-1 immunotherapy to patients with relapsed glioblastoma, the greater the benefit may be.

1. Introduction

Glioblastoma (WHO grade IV glioma, GBM) is the most common malignant brain tumor, that has aggressive biological behavior and resistance to treatment. Indeed, GBM (14.5% of all brain tumors and 48.6% of malignant brain tumors[1]) has an annual incidence from 0.6 to 3.7/100,000 individuals[2] and remarkably poor prognosis showing a 5-year survival rate of 4-5%[3]. Over the years, progress has been made in maximally possible surgical resection techniques, radiation therapy, and chemotherapeutic strategies, yet the current patients' median overall survival is around 15 months[4]. Although current therapy regimens have improved over the past 20 years, overall patient survival has not risen to the levels obtained for other solid tumors. Researchers continue to explore new treatments for glioblastoma.

Temozolomide(TMZ)is commonly used cytotoxic chemotherapies for newly diagnosed and recurrent GBM as well as lower-grade gliomas. They induce apoptosis and cell death by methylating guanine at the O6 position, initiating a double-strand break in the DNA, and cell cycle arrest[5, 6]. The O6-methylguanine-DNA methyltransferase (MGMT) protein removes the damaging alkyl groups from the O6 position of guanine and repairs the DNA. The alkylated protein is then degraded, requiring constant replenishment for DNA repair to be effective[6]. High expression of MGMT in cancer cells, account for the predominant mechanism of resistance to alkylating agents[7]. MGMT promoter methylation can silence MGMT that is associated with a favorable outcome after temozolomide chemotherapy in patients[8]. However, more than half of glioblastoma, the promoter is unmethylated, which means that these patients are resistant to TMZ. So, in the NCCN Guidelines (Central Nervous System Cancers) patients with unmethylated MGMT promoters are recommended to enter clinical trials to investigate whether there are better treatment options.

For the past few years, Immunotherapy has transformed the management of many cancers, and consequently there has been considerable investigation and research into immune-based therapeutic approaches for glioblastoma. The CNS has a unique immune microenvironment and was long thought to simply be an immune-privileged site[9]. However immune surveillance in the CNS and the role of myeloid cells is now known to be much more complex[10].In the context of metastatic cancer to the brain, immunotherapy has demonstrated significant efficacy. Suggesting that immunotherapy is not impeded by the blood-brain tumor barrier[11]. Treatment of GBM patients with immune checkpoint inhibitors may benefit. Animal study have shown that fractionated RT synergizes with PD-1 blockade to produce tumor regression and long-term survival in mice with orthotopic brain tumors[12].

More and more clinical trials on immunotherapy for GBM have been performed[13], and immune checkpoint inhibitors (ICIs) have received considerable attention. However, the efficacy and safety of PD-1/PD-L1 checkpoint blockade for glioblastoma patients remains unclear. Therefore, we performed a meta-analysis to access efficacy and safety. Nowadays, the randomized control trial about PD-1/PD-L1 checkpoint blockade without age restrictions in newly diagnosed GBM is rare. Thus, the studies we included were immunotherapy of Recurrent Glioblastoma.Studies of PD-1/PD-L1 checkpoint blockade immunotherapy combination with targeted therapy or chemotherapy were excluded. Study did not provide specific survival data or survival curve (Kaplan–Meier curve) was excluded.

2. Methods

2.1. Study eligibility criteria and selection

This study was prepared based on the preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines for reporting systematic reviews[14]. The study should be designed to evaluate the efficacy of PD-1/PD-L1 checkpoint blockade in recurrence GBM. Eligible patients enrolled should have normal hematologic, renal, hepatic function and have no restriction on age. Patients enrolled less than 10 were excluded because of relatively high bias.

2.2. Data sources and search strategy

The electronic database of PubMed, Web of Science, Embase and Cochrane Library were systematically searched from their inception to August 22, 2021. The search term comprised synonyms for “glioblastoma”, “Immunotherapy” and “PD-1/PD-L1 checkpoint blockade”. Reference lists of accepted studies and bibliographies of reviews were manually searched in order not to miss other relevant studies. Two investigators independently performed the literature search,

screened titles and abstracts, and selected relevant full articles and assessed their eligibility. Different opinions between two investigators were resolved by consensus or by consultation of a third investigator

2.3. Literature quality evaluation

It was inappropriate to evaluate literature quality using the Newcastle-Ottawa scale (NOS)[15] because most of the studies included were single arm trial. Referring to the NOS, we set some criteria to evaluate literature quality accommodating this study purpose and including:

- study population clearly defined;
- cohort representative for the population of recurrence GBM patients;
- therapeutic drug specifically defined;
- therapeutic dose specifically defined;
- clear and specific treatment process;
- follow-up long enough for outcomes to occur;
- adequacy of follow-up;
- assessment of outcome well performed;
- toxicities and comparison well recorded.

2.4. Data extraction

Clinical endpoints including PFS-6 (PFS rate at 6 months), OS-12 (OS rate at 12 months) were the primary survival data to extract. The incidence of severe acute/late toxicity, which were defined by Common Terminology Criteria for Adverse Events, were also extracted for additional analysis. When survival data only provided in survival curve (Kaplan–Meier curve), figures were digitised to extract numeric data using Engauge Digitizer.

2.5. Statistical analysis

Analyses were performed using R version 4.0 (<https://cran.r-project.org/>) with the “meta” package and Microsoft Excel 2019. The overall survival proportion was calculated with corresponding 95% confidence intervals (95%CI). Heterogeneity was assessed by calculating Cochran Q test and inconsistency index test (I² test). Random effects model was used in case of the existence of heterogeneity, defined as a P-value of Cochran Q test < 0.1 and I² > 50% [15], whereas fixed effects model was used in the opposite case. A two-tailed P-value < 0.05 was considered statistically significant.

3. Results

3.1. Search results

A total of 472 studies were identified after electronic and manual searches and after the removal of 15 duplicate articles, 472 articles remained. Then exclusion based on title and abstract, 73 full-text articles of potential interest were reviewed. After further evaluation, 7 prospective trials (contains 10 cohorts) were included in table. No additional articles were identified in reference lists of accepted studies and bibliographies of reviews. Fig. 1 shows a flowchart for procession of studies selection.

3.2. Study characteristics and quality evaluation

Referring to the NOS, we performed a particular literature evaluation scale to evaluate each study (Supplement Table S1). In general, the included studies could completely record important information of trial. However, the existence of prospective single arm trials made overall research somewhat heterogeneous and limited the quality of reporting.

3.3. OS

Overall survival was one of the primary clinical endpoints of interest in this study. A total of 343 patients in 7 trials (10 cohorts) provided survival data for recurrent glioblastomas treated with PD-1/PD-L1 checkpoint blockade immunotherapy. In these studies, the 1-year overall survival rates ranged from 19% to 69.0%. while the overall OS-12 rate was 40.0%(95% CI: 89.2% -95.1%) using fixed-effects model due to the heterogeneity (I²=49.10%, p=0.004) (Figure 2). Among, eight cohorts with adjuvant PD-1/PD-L1 checkpoint blockade for recurrent glioblastoma had 1-year survival rates of 19% to 58%, with heterogeneity between studies (I²=29%, P=0.2), and the overall OS-12 rate was 38% (95% CI: 0.32 to 0.44) using a fixed-effects model, see Figure 3. The only two remaining cohorts were neoadjuvant PD-1/PD-L1 checkpoint blockade immunotherapy for recurrent glioblastoma, with 1-year overall survival rates of 60%-69% for neoadjuvant PD-1/PD-L1 checkpoint blockade immunotherapy, with no heterogeneity between studies (I²=0%, P=0.63) and the overall OS-12 rate was 65% (95% CI: 0.46 to 0.81) using a fixed effects model (Figure 4)

3.4. PFS

Another important clinical endpoint, progression-free survival, was analyzed subsequently. For the PFS-6 rate, a total of 343 patients reached this clinical endpoint. Meta-analysis indicated the overall PFS-6 rate was 16.0% (95%CI 9%–23%) using random effects model determined by a heterogeneity (I²=51%, P=0.03) (Fig. 5). Similarly, 8 cohorts of adjuvant PD-1/PD-L1 checkpoint blockade immunotherapy for recurrent glioblastoma had PFS-6 rates ranging from 0% to 35%, with heterogeneity between studies (I²=35%, P=0.15), and overall PFS-6 rate was 13% (95% CI: 9%-17%) using a fixed-effects model, as shown in

Figure6. Two cohorts of neoadjuvant PD-1/PD-L1 checkpoint blockade immunotherapy had a 6-month progression-free survival range of 31%-40%, with no heterogeneity between studies ($I^2=0\%$, $P=0.63$) (Figure7).

3.5. Efficacy

Adjuvant anti-PD-1/PDL-1 immunotherapy for recurrent glioblastoma (1-year overall survival rates was 38%) better than bevacizumab for recurrent glioblastoma published by Henry S. Friedman et al[16], which had an 1-year overall survival rates was 24% ($p=0.02$). Adjuvant anti-PD-1/PD-L1 immunotherapy compared to physician's choice chemotherapy for relapsed glioblastoma[17] increased 1-year overall survival rates in patients by 18% (38% vs 20%, $p<0.001$). However, anti-PD-1/PDL-1 immunotherapy did not improve progression-free survival in patients with recurrent glioblastoma compared in comparison to bevacizumab or physician's choice chemotherapy(table2).

3.6. Safety and toxicity

The incidence of serious adverse events—grade 3 or greater AEs—in recurrent glioblastoma treated with adjuvant anti-PD-1/PDL-1 immunotherapy is approximately 25% [0.13; 0.40](Figure8)—compared to Henry S. Friedman et al.[16] 2009, which published an incidence of grade 3-4 adverse events of 46.4% for bevacizumab in recurrent glioblastoma, that is a significant lower ($p\text{-value} = 0.0002$). Unfortunately, in the study of physician's choice chemotherapy for recurrent glioblastoma published by Roger Stupp et al[17]. in 2012, the incidence of grade 3-4 adverse events was not given.

4. Discussion

Due to high invasiveness, the prognosis of glioblastoma is extremely poor even after receiving comprehensive treatments. Therefore, finding effective treatments to improve the prognosis of Glioma patients is an emerging issue. Researchers have constantly explored and tried new approaches for glioblastoma, but until now, only the new technique of Tumor-Treating Fields (TTF) has been shown to improve the prognosis of patients with high-grade glioma. However, TTF is currently not widely available in clinical practice in China due to its high expense. In recent years, with increasing research related to immune checkpoints, immunotherapy with PD-1/PD-L1 inhibitors has demonstrated durable and stable anti-tumors effects in a variety of tumors treatments. There are more and more clinical trials related to anti-PD-1/PDL-1 immunotherapy for GBM, but most of them are single-arm clinical studies, which cannot evaluate the efficacy Comparison against other anti-tumors treatments. Therefore, a single arm meta-analysis was done to assess how effective anti-PD-1/PDL-1 is in treating glioblastoma.

In this single arm meta-analysis show that immunotherapy is more effective and safer than chemotherapy or bevacizumab in the treatment of recurrent glioblastoma. Neoadjuvant anti-PD-1 immunization versus adjuvant anti-PD-1 immunization for recurrent glioblastoma shows superior efficacy, but also a higher incidence of grade 3-4 adverse events and higher toxicity. This also suggests that the earlier we apply anti-PD-1/PDL-1 immunotherapy to patients with relapsed glioblastoma, the greater the benefit may be.

However, this single-arm meta-analysis has a few limitations: firstly, the studies included in this meta are single-arm studies and the findings need to be further validated by randomized controlled clinical studies. Secondly, the inclusion of patients with recurrent glioblastoma in this meta is also somewhat biased, with some populations having a first recurrence and others having a second recurrence, and the prognosis in these two groups is inherently very different. Thirdly, the type and dose of anti-PD-1/PDL-1 drugs included in this meta also differed, which may also affect the prognostic assessment of patients with recurrent glioblastoma.

In general, this single-arm meta-analysis also provides some evidence of the benefits of PD-1/PD-L1 immunotherapy for recurrent glioblastoma. However, a higher level of evidence, such as randomized controlled clinical study, is still needed to confirm.

In addition, this meta-analysis appears that neoadjuvant immunotherapy for the recurrent glioblastoma has a superior 1-year OS rate for patients versus adjuvant immunotherapy. Suggesting that the earlier immunotherapy is applied to relapsed glioblastoma, the better the prognosis for the patients. Similar circumstances, does immunotherapy improves prognosis in newly diagnosed glioblastoma, especially in patients with unmethylated MGMT promoters? According to a clinical study published by Stupp Prof. et al[18], Median overall survival for patients with primary glioblastoma with unmethylated promoters was 11.8 months for radiotherapy alone and 12.6 months for radiotherapy combined with TMZ. Although the difference is statistically significant, it has little clinical benefit. This confirms that GBM with unmethylated MGMT promoter is inherently resistant to TMZ. How effective is the application of immunotherapy to newly diagnosed GBM with unmethylated MGMT promoters? 2019 ASCO Annual Meeting reported a study that MEDI4736 (durvalumab) + radiotherapy in patients with newly diagnosed unmethylated MGMT glioblastomas[19], Median OS was 15.1 (95% CI: 12.0, 18.4) months, clearly improved prognosis. Durvalumab + radiotherapy improved median OS by 3 months compared to radiotherapy alone for new unmeth GBM. Similarly, the efficacy is better than radiotherapy combined with TMZ for new unmeth GBM. Thus does RT+TMZ plus immunotherapy further improve the prognosis for patients with newly diagnosed glioblastoma? A clinical study was published on 2020 ASCO Annual Meeting that atezolizumab in combination with temozolomide (TMZ) and radiation in patients with newly diagnosed glioblastoma (GBM)[20], median OS was 17.1 months (95% CI: 13.9, not reached). median PFS was 9.7 months (95% CI: 7.6-15). Median survival was 14.6 months with radiotherapy plus temozolomide[4]. Therefore, RT+TMZ plus immunotherapy may further improve the prognosis of patients with newly diagnosed glioblastoma.

5. Conclusions

As far as we know, this study is the first systematic analysis to evaluate the efficacy of PD-1/PD-L1 checkpoint blockade immunotherapy in recurrence glioblastoma. In our meta-analysis uncovered that that immunotherapy offers new promising prognosis for newly diagnosed and relapsed glioblastoma patients, and the earlier we apply anti-PD-1/PDL-1 immunotherapy to patients with relapsed glioblastoma, the greater the benefit may be. The risk of toxicity

was tolerance. Further research including phase II/III random control trials to evaluate the efficacy of PD-1/PD-L1 checkpoint blockade immunotherapy in recurrence/newly diagnosed glioblastoma, and explore optimal schedule for recurrence/newly diagnosed glioblastoma .

Declarations

Availability of data and materials

No data, models, or code were generated or used during the study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Research involving Human Participants and/or Animals

This chapter does not contain any studies with human participants or animals performed by any of the authors.

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Tables

Table 1 The basic characteristics of clinical trials included in this meta-analysis.

Author	Year	Patients	Median age(range)	KPS		Drug and Dose	Re-RT	mOS (months)	mPFS (months)	OS-12 months	PFS-6 months
Antonio Omuro[21]	2018	10	58.5 (42–73)	≥70	adjuvant	Nivolumab 3 mg/kg Q2W	NOT	10.4	1.9	40%*	12%*
Antonio Omuro[21]	2018	10	57 (37–68)	≥70	adjuvant	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W	NOT	9.2	1.5	30%*	0*
Antonio Omuro[21]	2018	20	60 (27–73)	≥70	adjuvant	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W	NOT	7.3	2.1	33%*	15%*
Rimas V. Lukas[22]	2018	16	52[31-75]	≥70	adjuvant	atezolizumab 1200mg	NOT	4.2 months (range 1.2 - 18.8+ months)	1.2 months (range 0.7–10.7 months)	21% (95% CI 0.3–42.6)	6.25%*
Timothy F. Cloughesy[23]	2019	16	59.3	86 ± 6.2	adjuvant	pembrolizumab 200 mg Q3W	NOT	7.5 months	2.4 months	29%*	13%*
David A. Reardon[24]	2020	184	55.5 (22-77)	80	adjuvant	Nivolumab 3 mg/kg Q2W	NOT	9.8 months	1.5 months	41.8%	15.7%
Lakshmi Nayak[25]	2020	30	55 (42, 62)	≥70	adjuvant	Pembrolizumab (200 mg) Q3W	NOT	10.3 months	1.4 months	30%	6.7%
David A. Reardon[26]	2021	26	55.5 [33-76]	ECOG:0-1	adjuvant	pembrolizumab 10 mg/kg Q2W	NOT	13.1 months	2.8 months	58%	37.7%
Timothy F. Cloughesy[23]	2019	16	55.4	80 ± 8.9	Neoadjuvant	pembrolizumab 200 mg Q3W	NOT	13.7 months	3.3 months	69%*	33%*
John de Groot[27]	2020	15	54	≥70	Neoadjuvant	pembrolizumab 200 mg Q3W	YES	20.3 months	4.5 months	63%	40%

Table 2 :Comparison of various clinical endpoints between immunotherapy and BPC/BEV

Treatment	OS-12		PFS-6	
	n	rate	n	rate
BPC	117	20%	117	15%
adjuvant PD-1	312	38%	312	13%
P-value	0.001		0.7	
BEV	85	24%	85	42.60%
adjuvant PD-1	312	38%	312	13%
P-value	0.02		0.001	
neoadjuvant	31	65%	31	35%
adjuvant PD-1	312	38%	312	13%
1. Value	0.0069		0.008	

Figures

Figure 1

Shows a flowchart for procession of studies selection.

Figure 2

The 1-year overall survival rates ranged from 19% to 69.0%. There was moderate between-study heterogeneity ($I^2=49.10\%$, $p=0.004$) and a combined 1-year survival rate of 40% (95% CI: 39.2%-49.1%)

Figure 3

Adjuvant PD-1/PD-L1 checkpoint blockade for recurrent glioblastoma had 1-year survival rates of 19% to 58%, with heterogeneity between studies ($I^2=29\%$, $P=0.2$), and a combined 1-year survival rate of 38% (95% CI: 0.32 to 0.44) using a fixed-effects model

Figure 4

Neoadjuvant PD-1/PD-L1 checkpoint blockade immunotherapy for recurrent glioblastoma had 1-year overall survival rates of 60%-69% for neoadjuvant PD-1/PD-L1 checkpoint blockade immunotherapy, with no heterogeneity between studies ($I^2=0\%$, $P=0.63$) and a combined 1-year survival rate of 65% (95% CI: 0.46 to 0.81) using a fixed effects model

Figure 5

The overall PFS-6 rate was 16.0% (95%CI 9%–23%) using random effects model determined by a heterogeneity ($I^2=51\%$, $P=0.03$).

Figure 6

Adjuvant PD-1/PD-L1 checkpoint blockade immunotherapy for recurrent glioblastoma had PFS-6 rates ranging from 0% to 35%, with heterogeneity between studies ($I^2=35\%$, $P=0.15$), and overall 6-month progression-free survival rate of 13% (95% CI: 9%-17%) using a fixed-effects model.

Figure 7

Neoadjuvant PD-1/PD-L1 checkpoint blockade immunotherapy had a 6-month progression-free survival range of 31%-40%, with no heterogeneity between studies ($I^2=0\%$, $P=0.63$) .

Figure8

Figure 8

The incidence of serious adverse events—grade 3 or greater AEs—in recurrent glioblastoma treated with adjuvant anti-PD-1/PDL-1 immunotherapy is approximately 25% [0.13; 0.40].

Supplementary Files

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- [SupplementTableS1.xlsx](#)