Efficacy and Safety of Immunotherapy and Standard of Care in High-Grade Gliomas: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND: Immunotherapy combined with standard of care (SOC) is often used for high-grade glioma (HGG). There are few comparisons about immunotherapy with or without SOC treatment (IMT) versus SOC. It is important to understand what interventions exist and their relative effectiveness. **METHODS:** The Cochrane Library, Embase, Medline, and the Web of Science Core Collection were systematically searched by two librarians. Retrieved hits were screened for inclusion. Subgroup analysis was used to examine main factors associated with overall survival (OS). Progression-free survival (PFS), objective response rate (ORR), and occurrence rate of adverse events (AE) as primary endpoints were used to assess the efficacy and safety of IMT. This study was registered with PROSPERO, number CRD42019112356. **RESULTS:** The search yielded 2315 results of which 11 met eligibility criteria. We identified 11 publications. Compared to SOC alone, IMT improved OS (HR = 0.62, 95% CI 0.48-0.81; $p = 0.0003$), PFS (HR = 0.59, 95% CI 0.39-0.89; $p = 0.0117$), ORR (RR = 3.12, 95% CI 1.09-8.95; $p = 0.034$). But it increased the occurrence rate of AE (RR = 1.56; $p < 0.0001$). **CONCLUSIONS:** It suggests that IMT compared to SOC has a certain effectiveness. Our findings support the use of immunotherapy in brain tumor to improve HGG outcomes.

Background

Malignant tumors occupied 32.8% in primary brain and central nervous (CNS) system. High-grade gliomas (or malignant gliomas) account for approximately 80.5% of the 24,560 new cases of malignant primary brain and CNS tumors in the United States each year[1]. High-grade gliomas (HGG), mainly anaplastic astrocytoma (AA; WHO grade III) and glioblastoma multiforme (GBM; WHO grade IV) [2, 3]. Glioblastomas account for approximately 50 to 60% of malignant gliomas[1]. HGG has long been a concern in the society. The median overall survival (OS) times of SOC (TMZ combined with radiotherapy) were 14.6 months for newly diagnosed GBM (WHO grade IV)[4], 7.4 months for recurrent Grade IV gliomas, and 11.4 months for recurrent Grade III gliomas[5].

Despite remarkable advances in neurosurgery, radiotherapy and chemotherapy, HGG patients still face a poor prognosis. Standard of care for HGG usually entails surgery followed by maximal surgical resection, followed by radiotherapy plus concomitant and adjuvant temozolomide (TMZ) chemotherapy, sometimes including carmustine and PCV (Procarbazine+CCNU+Vincristine) scheme as alternative chemotherapy or bevacizumab as targeted-therapy. Influenced by O-6-methylguanine-DNA methyltransferase (MGMT) promoter, about 55% GBM patients could't benefit from TMZ[6]. Microsatellite instability (MSI) arise in GBM during TMZ therapy and mediate TMZ resistance[7]. Resistance to chemotherapy of HGG appears to another concerning issue. The possible susceptibility of HGGs to IMT has been explored.

The concept of cancer immunotherapy can be tracked back to William Coley who first use bacteria to cure cancer in 1891[8]. It means that the immune system can recognize and control tumor growth. In recent years, immunotherapies are gaining much research attention and exceedingly more evidences show that high grade gliomas can get certain benefits from it[9]. Six meta-analysis respectively published in 2014 and 2018 indicated improved OS and PFS were obtained applying immunotherapy in HGG patients [10–15]. As far as we known, our context is first meta-analysis to do such detailed subgroup-analyses. Nonetheless, we also use some more stringent criteria to decrease the possible difference from clinical background.

The interventions of current systematic review included immunotherapy categorized as follows:

1. Dendritic cell (DC) vaccination
2. Viral vector-based vaccines (AdvHSV-tk, PVSRIPO)
3. Immunopotentiator: TGF- β_2 inhibitor, Cpg-ODN

In order to verify and quantify the efficacy and safety of the combination of immunotherapy and SOC, current meta-analysis was started by utilizing survival data of published papers. We also hope to inform clinicians which kind of IMT is more effective than SOC for HGG patients.

Methods

Search strategy and selection criteria

For this systematic meta-analysis, we searched for randomized controlled trials (RCTs) published from the date of database start to December 1, 2018, comparing immunotherapy combined SOC treatment (IMT) and standard of care (SOC) in adults (age ≥ 18), with a diagnosis of HGG according to standardized diagnostic criteria.

Two authors (S.N. Zhang and X.D. Hu) searched online using thematic and free words as a strategy through the Cochrane Library/Embase/Pubmed/Web of science four libraries for relevant articles published up to December 1, 2018. Search terms included "glioma", "astrocytoma", "glioblastoma", "immunity", "immunotherapy", "viruses", "humans" and "randomized". An English language restriction was pronounced. Clinical trials registered on the website (<http://ClinicalTrials.gov>) were also explored.

The following inclusion criteria have been adopted: therapy intervention restricted in IMT, adults with HGG, two arms with IMT and SOC. SOC entails surgery, radiotherapy, or chemotherapy. All included studies are English.

The following exclusion criteria have been adopted: lack of relevant outcome data, trials with non-standard of care control arm, phase I trials, phase II single arm trials, animal or cell trials. Abstracts and presentations from all major conference proceedings were excluded.

Data extraction and quality assessment

Two investigators (X.Y. Peng and X.M. Liu) extracted relevant information from the included articles. The HR described as a more suitable measure for analyzing time-to-event outcomes than odds ratio (OR) or relative risk (RR) was extracted [16, 17]. When report of HR and 95 % CI was not available, estimated value was derived indirectly from Kaplan–Meier curves according to the methodology described by Jayne F Tierney[16]. Censored dots in graphic data were extracted by software Engauge Digitizer 4.1 (<http://digitizer.sourceforge.net/>).

Objective response rate and occurrence of adverse events was extracted by amount of incidents in experiment group and control group. Adverse events were only included that assessed as Grade II/III/IV according to National Cancer Institute – Common Toxicity Criteria (NCI-CTC).

Statistical analysis

Details of our statistical analyses were performed by R (version 3.6.1 for Windows; <https://www.r-project.org/>). Specific methods of operation could be found [18].

The primary end point was overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and occurrence rate of adverse events (AE); secondary end points were subgroup analysis, meta regression, heterogeneity exploration and cumulative meta-analysis.

Hazard ratio and 95% confidence intervals (CIs) were calculated for OS and PFS. Risk ratios and 95% CIs were calculated for ORR and AE. A random-effects model was used for data synthesis in the presence of significant heterogeneity, while a fixed-effects model was used when there was no significant heterogeneity. Heterogeneity across trials was assessed with I^2 test, and $I^2 > 50\%$, $p < 0.1$ suggested there was significant heterogeneity.

Subgroup analysis was conducted. Heterogeneity across entire study were examined by galbraith radial plot.

Sensitivity analysis was performed to explore the impact of an individual study by deleting 1 study each time. Publication bias was examined by funnel plots.

Results

Trial selection

Overall, 2,315 citations were identified by the researchers and 66 potentially eligible articles were retrieved in full text. We excluded 55 reports, but included 4 additional studies from other sources, resulting in 11 publications describing 10 RCTs published and 6 historical-matched control trials (HMCTs) between 2004 and 2018 (Figure 1).

Main Characteristics of studies

1,288 participants who are conformed HGG by clinical, radiological or MRI evidence were including in this study. 67 participants were diagnosed AA/AO/Others (WHO grade III). 1,221 participants were diagnosed GBM (WHO grade IV).

We cover AdvHSV-tk+ GCV/DC vaccine/TGF- β_2 inhibitor Trabedersen/Cpg-ODN/ recombinant nonpathogenic polio–rhinovirus chimera (PVSRIP0) in this context, and focus on the need for intimately understanding the efficacy and safety of immunotherapy in HGG adults. We classified these study into viral therapy (AdvHSV-tk+ GCV/PVSRIP0), DC therapy, and immunopotentiators (Trabedersen/Cpg-ODN). Thereof 624 participants were provided with immunotherapy. Mean study sample size was 81, participants ranging from 13 to 250.

In viral therapy studies, five were without TMZ as a kind of SOC and six were with TMZ. Totally 931 participants were recruiting in viral therapy studies (393 patients in experimental arm and 538 patients in control arm). Three studies reported PFS and eleven studies reported OS . Details could be found in Table 1. As for DC therapy, there were three studies in DC therapy. And all studies used TMZ in SOC. 90 participants were recruiting in DC therapy (43 patients in experimental arm and 47 patients in control arm) (Table 2). Immunopotentiator(IP) was used in two studies with TMZ as one of SOC as experimental arm (88 patients in experimental arm and 179 patients in control arm (Table 1).

Primary endpoints

OS

We apply random-effect to assess efficacy of immunotherapy through HR of OS. A total of 1,288 participants in 16 studies were included in this meta-anlysis (524 patients treated with immunotherapy, 764 patients treated with standard of care). It shows that IMT could decrease the risk of death by 38% compared with SOC (HR = 0.62, 95% CI 0.48-0.81; $p = 0.0003$). Substantial heterogeneity was found ($\tau^2=0.15$, $p < 0.01$; $I^2= 64.7\%$) (Figure 1B). Moreover, three subgroups were divided according to IMT type (Figure 1B). Subgroup of DC therapy and immunopotentiator both have no heterogeneity (respectively, $I^2=0$, $p=0.58$; $I^2=0$, $p=0.40$). Yet viral therapy presents comparatively high heterogeneity ($I^2=69\%$, $p < 0.01$).

PFS

With respect to PFS, we used random-effect to assess efficacy of immunotherapy through HR of it. We pooled six trials, a total of 316 participants (113 patients treated with IMT, 203 patients treated with SOC). It shows that IMT could decrease the risk of recurrence by 41% compared with SOC (HR = 0.59, 95% CI 0.39-0.89; $p = 0.012$). Significant heterogeneity was found ($\tau^2 = 0.166$, $p = 0.018$; $I^2=62.9\%$) (Figure 1A). Besides, two subgroups were divided according to intervention type (IMT with SOC or IMT alone), which decrease heterogeneity significantly (Figure 1B). It demonstrates that IMT alone (HR = 0.30, 95% CI 0.17-0.52; $I^2=0$) may be better to prolong PFS than IMT with SOC (HR = 0.79, 95% CI 0.57-1.10; $I^2=33.3$)

ORR

We used fixed-effect to assess efficacy of IMT by ORR. Only one trial reported ORR. But it reported ORR according to different type of HGG. So we divided it into 3 studies. It shows that tumor lesion in IMT group was significant compared to SOC (RR=3.12; 95% CI 1.09-8.95; $p = 0.034$). Little heterogeneity was found ($\tau^2 = 0.581$, $p = 0.232$; $I^2=31.5\%$) (Figure 1C).

AE

As for safety of immunotherapy regimen, there are 6 studies reported some adverse events (AE) according to NCI-CTC including neutropenia (59.2%), liver function tests alterations (40.6%), and seizure (22.4%), lymphopenia(21.9%) have a relatively high incidence. In addition to them, other adverse events also existed. We used random-effect to assess safety of immunotherapy through RR of occurrence rate of AE. It shows significant difference between immunotherapy arm and SOC arm (RR = 1.67; 95% CI 1.15-2.44; $p < 0.0001$) and substantial heterogeneity ($\tau^2=0.400$, $p=0.001$; $I^2=52.5\%$) (Figure 1D). It reveals that immunotherapy existed a certain potential safety problem.

Secondary endpoints

Considering substantial heterogeneity within studies, we explore the source in several ways. We dedicated to decrease the heterogeneity and make our context homogeneity.

Galbraith radial plot

We drew Galbraith radial plot and found some studies including Ji(1)(2)/cho2012/Westphal2013/Rainov2000 fell outside the 95% confidence interval line. Thereof, Ji(1)(2) and cho2012 carried out in China, Westphal2013 and Rainov2000 was in a background that TMZ has not been widely applied. It hinted that recruiting area and TMZ applying may have some effect in heterogeneity between studies. (Figure 1E)

Main factors influencing efficacy

Besides exploring the source of heterogeneity, we also try to find out factors influencing efficacy of IMT. (Table 4)

As mentioned above, subgroups divided according to IMT type manifested a statistically difference among viral therapy, DC vaccine and immunopotentiator ($p < 0.05$).

In addition, we divided all studies reported OS in terms of recruiting area(Europe/China/USA) and deleting two multi-area studies[19, 20], which significantly decreased heterogeneity. What's more, it also suggested that recruiting area may be a main factor for efficacy of IMT ($p < 0.05$; Figure 2A). Forest plot before deleting two studies can be found in Supplementary Fig. 4.

Besides, subgroup analysis in accordance with TMZ applying was done(TMZ/Not TMZ/Not TMZ partly) as galbraith radial plot indicating. After subgroups divided, heterogeneity was decreased respectively. And pooled HR effective value was statistically different among subgroups ($p < 0.05$).

Furthermore, IMT was defined as immunotherapy with or without SOC treatment. The former means IMT was used as an adjuvant, while the latter means IMT was used as a new therapy. We also found no matter as an adjuvant or as a new therapy, immunotherapy has a certain effect to prolong the OS of HGGs. But when it was used alone, the confidence interval is larger.

At last but not least, whether studies are randomized-controlled or double-bind trials doesn't have statistically significance to effective value ($p > 0.05$). Gliomas whether recurrent or not, and whether Grade III or IV are does not have statistically significance to effective value, too($p > 0.05$) (Figure 2B).

Sensitivity analysis

Sensitivity analysis was done to assess which study contributes to influence our current results. We didn't find any study which have a potential impact on results, and the results did not materially change by deleting any study at a time (Figure 4C).

Publication bias

Publication bias was explored with an inverted funnel plot, which showed a significant asymmetry around 95% CI and Begg's test showed a significance of bias ($p < 0.001$). We used trim-and-fill method to identify the publication bias. However, the random effect value became larger (HR = 0.92; 95% CI 0.71-1.20).

Discussion

Immunotherapy is playing a more and more important role in the treatment of tumor, which maximize the retention of non-cancerous cells and kill cancer cells. After amounts of attempts, immunotherapy gradually earned a place as one of first/second-line treatments. However, several kinds of immunotherapy exists there. Which kinds of immunotherapy behaves better in the treatment of high-grade glioma is a question among many clinicians and researchers.

We did a systematic review of the efficacy and safety of IMT and SOC in adult HGG patients. The present results have shown that IMT yields better results compared to SOC, despite it may have potential risk to increase adverse events.

The golden standard in clinical is OS. We utilize this to compare the efficacy of IMT and SOC. In our context, the order of efficacy of various IMT is like this: DC therapy > oncolytic virus with the suicide gene > immunopotentiator. Why does DC therapy behave best? Why are there no checkpoint inhibitors? We

considered about it. Some researches about MSI and TMB could explain. TMB and MSI could be biomarkers to identify HGG patients who may benefit from immunotherapy. HGGs in adults have lower MSI than pediatric HGGs ($p < 0.05$) [21]. In addition, another study found no statistically significant association among TMB, influx of cytotoxic CD⁸⁺ T cells, and immune checkpoint expression[22]. Nonetheless, it demonstrates that TMB is associated with WHO tumor grade. That explained no statistical difference among different clinical type of HGGs (Figure 3B) in our context. A high TMB usually results in more tumor antigens and neoantigens, which leads to increased tumor immunogenicity. Albeit low TMB and MSI in HGGs, this only resolve the question why there are no phase II or III studies about checkpoint inhibitors. Forecasting the future of immunotherapy in HGGs, DC therapy (which produce more antigens) , oncolytic virus(stimulates strong immune) have promising develop space. For bad results of prolonging OS applying immunopotentiator, they claimed that their negative result was unexpected and it may be explained by a selection bias of patients enrolled in recurrent GBM and the different mode of administration of CpG-28 in Renata Ursu et al.'s study [23].

According to current clinical trials,, we found different kinds of immunotherapy, TMZ whether is applied in the treatment of standard of care, and patients recruiting area may affect results based on subgroup analysis of OS. In addition, whether adopting the double-blind methods in trials may have effect on results ($p = 0.077$). Thus, we appeal to more double-blind trials' advent.

As for PFS, it is an endpoint increasingly recognized by researchers recently. When there is no significant improvement in OS, as an alternative outcome, PFS could help to explain the underlying efficacy. Nonetheless, trials reported PFS in our study are lacking. Limited studies indicated that IMT, compared to SOC, could decrease the risk of recurrence over SOC.

ORR is another powerful evidence of effectiveness. It was defined as follows: the proportion of patients who achieved more than 50% tumor lesion. Our study shows that tumor lesion in the IMT group was significant compared to SOC in the 14th month after the first treatment. Until the 6th month, IMT and SOC hadn't have statistical difference($p > 0.05$).

For significant publication bias examined by Begg's test, the possibility of positive publication cannot be ruled out. For the number of incorporated studies is insufficient, we should have serious reservations about the evaluation of the efficacy and safety. We hope it comes to an agreement about them in the future. What's more, the safety of IMT is a problem open to question. We found there is some potential harm to the human body.

Because of the certain heterogeneity existing, its sources are explored. Through subgroup analyses, we found dividing according to patients recruiting area can decrease heterogeneity rapidly. Within subgroup, there are no significant heterogeneity. China benefit mostly. We guess that racial difference and regional lifestyle maybe important causes , despite no comprehensive studies have explored the causes.

Besides, researchers have been made efforts to accelerate precision medicine. Yao 2018 et al (DC therapy) found IDH^{WT} TERT^{MT} has better efficacy in GBM IMT group [24]. However, Annick 2018 et al (viral therapy) confirmed that the mutation form, IDH R132, in GBM IMT group has no survival advantage[25]. The efficacy of MGMT status applying immunotherapy was only reported in one article Ursu 2017 et al (immunopotentiator), It shows no statistically difference between groups[23].

Moreover, a meta-analysis about it also suggests that immunotherapy has a tail-dragging effect so that use it early could have better results[26]. In the future, we hope more trials about it could emerge out of, and then we will update our reviews aiming at it.

Abbreviations

SOC: standard of care, such as surgery, chemotherapy, and radiotherapy; IMT: immunotherapy combined SOC treatment OS: overall survival; PFS: progression-free survival; ORR: objective response rate; AE: adverse events; GBM: glioblastoma; TMZ: temozolomide; CNS: central nervous system; HMCTs: historical-matched control trials; NOS: Newcastle Ottawa quality assessment; AA: anaplastic astrocytoma; HGG: high-grade glioma; DCV: dendritic cell vaccine; PVSRIPO: recombinant nonpathogenic polio–rhinovirus chimera; MGMT: O-6-methylguanine-DNA methyltransferase MSI: microsatellite instability; TCGA: The Cancer Genome Atlas; NCI-CTC: National Cancer Institute – Common Toxicity Criteria.

Declarations

Ethics approval and consent to participate

This study is a systematic review and meta-analysis that provides secondary research evidence. The ethics is not applicable. Also, the consent is unable to be obtained because the patients are not traceable. However, all the information is sufficiently anonymized. Details have been removed from the case descriptions to ensure anonymity. The editors and reviewers have reviewed the available details and are satisfied that the information supports the authors' conclusions.

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Availability of data and materials

Data supporting the conclusions of this study are provided within the manuscript. Raw data is available from PROSPERO, number CRD42019112356.

Authors' contributions

Shengnan Zhang conceptualized formal analysis and screened literature. Libo Xu, Guanyu Chen and Qian Wang took part in revision and writing instructions. Jiangmin Liu was responsible for statistical analysis. Xindan Hu screened literature. Naiyan Wen and Xiaomin Liu extracted data from literature.

Xinyu Peng and Lei Fan assessed risk of bias. Baofeng Guo and Ling Zhang provided with instructions on methodology.

Ethical approval

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

Consent to publish

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Table

0	First author(year)	Method	NCT number	Phase	Patients(E/C)	Blind	Median Age(E)	Median Age(C)	Intervention	Control	KPS score	Region	Patients Characteristics	Follow up Time
TMZ is NOT in SOC	Rainov 2000[29]	Randomized	N/A	III	124/124	Open-label	60.2	58.3	AdvHSV-tk+GCV +SOC	SOC	≥70	Europe	Newly diagnosed GBM	21.6
	Immonen 2004[24]		N/A	II		Open-label	51.9	56.5	AdvHSV-tk+GCV+SOC	SOC	≥70	Europe	GBM=31; AA=5	
	Immonen 2004(1)	Randomized			17/19								PR/REC HGG	56
	Immonen 2004(2)	Historical			17/36								PR/REC GBM	44
	Immonen 2004(3)	Historical			13/18								PR/REC HGG	56
	Immonen 2004(4)	Randomized			13/34								PR+REC GBM	44
TMZ is in SOC	Westphal 2013[1]	Randomized	2004-000464-28 ^a	III	119/117	Open-label	58	57	AdvHSV-tk+GCV	SOC	≥70	Europe	Newly diagnosed GBM	14
	Ji 2015[23]			II		Open-label	49	54	AdvHSV-tk+GCV	SOC	N/A	China	GBM=32 AA/others=12	60
	Ji 2015(1)	Randomized			22/22								Recurrent HGG	
	Ji 2015(2)	Randomized			14/18								Recurrent GBM	
	Wheeler 2016[28]	Historical	NCT00589875	II		Open-label	57	60	AdvHSV-tk+GCV +SOC	SOC	≥70	USA	GBM=171;AA/AO=11	60
	Wheeler 2016(1)				43/128								Newly diagnosed HGG	
	Wheeler 2016(2)				48/136								Newly diagnosed GBM	
	Annick 2018[18]	Historical	NCT01491893	IV	61/104	Open-label	55	55	PVSRIPO+Bev	SOC	≥70	USA	Recurrent GBM	27.6

Table 1. Main Characteristics of studies that use viral therapy for the treatment of HGGs. Follow-up Time, months; EMOS, experimental group median overall survival time, months; CMOS, control group median overall survival time, months; EMPFS, experimental group median progression-free survival time, months; CMPFS, control group median progression-free survival time; a: EudraCT number; PVSRIPO, recombinant nonpathogenic polio–rhinovirus chimera; HGG, high-grade glioma; GBM, glioblastoma; PR/REC: Primary or recurrent; Bev, Bevacizumab.

	First author(year)	Method	NCT number	Phase	Patients(E/C)	Blind	Median Age(E)	Median Age(C)	Intervention	Control	KPS score	Region	Patients Characteristics	Follow up Time
TMZ is in SOC	Cho 2012[2]	Randomized	N/A	II	18/16	Open-label	58	58.5	DCV+SOC	SOC	>70	China	Newly diagnosed GBM	15
	Vik-mo 2013[25]	Historical	NCT00846456	N/A	6/7	Open-label	57	55.9	DCV+SOC	SOC	N/A	Europe	Newly diagnosed GBM	13
	Yu Yao 2018[17]	Randomized	NCT01567202	II	22/21	Double Blind	48	50	DCV+SOC	Placebo+SOC	≥60	China	PR/REC GBM	1

Table 2. Main Characteristics of studies that use DC therapy for the treatment of HGGs. Follow-up Time, months; EMOS, experimental group median overall survival time, months; CMOS, control group median overall survival time, months; EMPFS, experimental group median progression-free survival time, months; CMPFS, control group median progression-free survival time; HGG, high-grade glioma; GBM, glioblastoma; PR/REC: Primary or recurrent.

	First author(year)	Method	NCT number	Phase	Patients(No.)E/C ^a	Blind	Median Age(E)	Median Age(C)	Intervention	Control	KPS score	Region	Patients Character
TMZ is in SOC	Ursu 2017[20]	Randomized	NCT00190424	II	39/42	Double Blind	62.0	59.0	CpG-ODN+SOC	SOC	≥60	Europe	Recurrent GBM
	Bogdahn 2011[2]	Randomized	N/A	IIb	27/12	Open-label	39.0	40.0	TGF-β2 inhibitor(Trabedersen)	SOC	≥70	Europe	Recurrent AA=39
					62/33		56.5	45.5					Recurrent GBM=95

Table 3. Main Characteristics of studies that use immunopotentiator therapy for the treatment of HGGs. Follow-up Time, months; EMOS, experimental group median overall survival time, months; CMOS, control group median overall survival time, months; EMPFS, experimental group median progression-free survival time, months; CMPFS, control group median progression-free survival time; HGG, high-grade glioma; GBM, glioblastoma; PR/REC: Primary or recurrent.

Variable	No. of Studies	No. of Participants		OS, HR(95%CI)	I ² value(%)	p value ^b
		IMT ^a	Ctrl			
Therapy type						
DC vaccine	3	43	47	0.38 [0.21;0.68]	0	0.007*
Immunoactivator	2	88	179	1.12 [0.75;1.68]	0	
Viral therapy	11	493	755	0.62 [0.47;0.83]	68.5	
Intervention type						
With SOC	11	363	666	0.62 [0.46; 0.84]	59.6	0.919
Alone	5	261	315	0.60 [0.35; 1.05]	77.3	
SOC type						
TMZ	10	319	632	0.54 [0.39; 0.76]	56.8	0.003*
Not TMZ	5	181	223	0.67 [0.43; 1.03]	58.1	
Not TMZ[partly]	1	124	126	1.18 [0.86; 1.61]	/	
Stage						
Newly diagnosed GBM	4	186	269	0.60 [0.30; 1.18]	74.9	0.539
Primary/Recurrent HGG	2	30	37	0.54 [0.32; 0.92]	0	
Primary/Recurrent GBM	3	51	92	0.47 [0.30; 0.74]	0	
Newly diagnosed HGG	2	172	260	0.86 [0.44; 1.70]	79.8	
Recurrent GBM	3	123	256	0.70 [0.36; 1.35]	78.5	
Recurrent HGG	1	22	22	0.31 [0.14; 0.67]	/	
Recurrent AA	1	40	45	0.72 [0.24; 2.17]	/	
Study Design						
Historical control	10	188	427	0.60 [0.47; 0.77]	0	0.838
Randomized	6	436	554	0.63 [0.44; 0.91]	73.1	
Recruiting area						
China	4	73	80	0.69 [0.50; 0.97]	25.1	0.010*
USA	3	452	366	0.31 [0.21; 0.48]	0	
Europe	7	154	293	0.63 [0.48; 0.84]	0	
Label type						
Open-label	13	431	699	0.56 [0.42; 0.74]	55.8	0.077
Double Blind	3	193	282	0.93 [0.57; 1.54]	69.9	

Table 4. Subgroup Analysis of IMT and Death Incidence for Each Variable. ^a IMT: Immunotherapy; ^b p value for subgroup differences (random effects model)

Supplementary File Legend

Supplementary Figure 1. Factors may influence the efficacy of IMT. **A**, subgroups divided according to IMT whether combined with SOC. **B**, subgroups divided according to SOC whether include TMZ. **C**, subgroups divided according to trials whether apply randomized-control. **D**, subgroups divided according to trials whether apply double-blind.

Supplementary Figure 2. Galbrith radial plot presented with name.

Supplementary Figure 3. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart of search strategy

Supplementary Figure 4. Subgroup analysis in accordance with recruiting area before deleting two studies.

Figures

Figure 1

Although IMT has some adverse effects, it has a certain effect on prolonging survival and controlling tumor growth. **A**, Forest plot for PFS. **B**, Forest plot for OS. **C**, Forest plot for ORR. **D**, Forest plot for AE. Studies are listed on the left and HR with 95% CI are on the right. Box sizes are inversely proportional to the standard error of the study; therefore, larger boxes indicate greater weight of the trial in the meta-analysis estimation. **E**, Galbraith radial plot. Plot the inverse of the normalized estimate with respect to its standard error. If the point is close to the slope of the scatter, it means homogeneity.

Figure 2

Potential source of heterogeneity. A, subgroup analysis in accordance with recruiting area. B, subgroup analysis in accordance with types of glioma. C, sensitivity analysis diagram. After deleting one study at a time and leaving the others the same, to observe which ones have a significant potential impact on the results.

Figure 3

Funnel plot presenting the association between OS and publication bias.

Supplementary Files

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