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ORIGINAL ARTICLE / META-ANALYSIS

Efficacy and safety of immunotherapies for the treatment of high-grade gliomas: a systematic review and meta-analysis

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Abstract

Background/Aim: High-grade gliomas are aggressive brain neoplasms usually refractory to treatment. Recently new treatment approaches have emerged, including immunotherapies. Hence, the aim of the present study was to evaluate the efficacy and safety of immunotherapies in adult patients with high-grade gliomas. **Methods:** Searches were performed in three databases for relevant studies published until December 2020. Title and abstract screening, full-text review, data extraction, and risk of bias assessment were performed independently by two reviewers. Risk of bias assessment was performed according to the revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Meta-analyses were performed with Review Manager software (version 5.4.1), using risk ratio and 95% confidence intervals as measure of effect, the Mantel-Haenszel method, and random effects models. The quality of evidence assessment was conducted according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. **Results:** Nineteen studies were included in the systematic review, of which 15 reported comparable data for meta-analyses. The outcomes assessed in the meta-analyses were overall survival (OS) and progression-free survival (PFS), with subgroups at 6, 12, and more than 12 months. No statistical differences were observed between immunotherapy and conventional treatment, except for the OS subgroup over 12 months. The certainty on the evidence was moderate. **Conclusion:** There was no evidence of an additional benefit of immunotherapy compared to standard treatment in the synthesis of results from clinical trials. Further high-quality clinical trials are needed to improve the quality of evidence concerning immunotherapies for the treatment of high-grade gliomas.

Keywords: High-grade gliomas; Immunotherapy; Meta-analysis; Systematic review; Overall survival; Progression-free survival

How to cite

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INTRODUCTION

High-grade gliomas are brain malignancies with aggressive behaviour which, for the most part, become refractory to oncologic treatment. According to the 2016 World Health Organization (WHO) revised classification of central nervous system (CNS) tumours, oligodendroglial and diffuse astrocytic gliomas of adulthood are classified from grades II to IV based on the presence of histological features known to correlate with the natural course of the disease[1].

Glioblastoma (GBM), categorized as a grade IV CNS tumour, is the most common malignant tumour of the CNS (47.7%), with a rate of 3.21 per 100,000 individuals according to CBTRUS Statistical Report withinside the United States in 2011-2015[2]. GBM is the maximum competitive and infiltrative mind tumour, with a 5-yr typical overall survival (OS) rate of only 5.6% after diagnosis[2]. The general treatment method for GBM is maximal safe resection, associated with radiation therapy and chemotherapy[3].

Tumour recurrence happens in nearly all patients. The treatment alternatives for recurrence consist of repeat surgical cytoreduction, radiation therapy, and chemotherapy, such as temozolomide, lomustine, bevacizumab, etoposide, and procarbazine. However, there's no worldwide standard, and the prognosis is poor[4]. In huge patient collection and medical trials, median OS instances withinside the range of 6–9 months from the time of first development or recurrence had been achieved[5]. Most recurrent tumours were formerly uncovered to genotoxic pressure from irradiation and/or chemotherapy; therefore, they may be expected to have a higher mutational burden and more immunogenicity than untreated tumours[6].

The advent of immunotherapy was a breakthrough in cancer management, particularly for solid malignancies (e.g., non–small cell lung cancer), in which drugs targeting components of immunological system, such as checkpoint inhibitors, were able to improve patients' overall survival. Despite the promising results for solid tumours the evidence regarding immunotherapy benefits in patients with high-grade gliomas is still scarce and not conclusive. Currently, several clinical trials are being conducted to better understand the role of immunotherapeutic approaches (e.g., checkpoint inhibitors, monoclonal antibodies, vaccines, chimeric antigen receptor (CAR) T-cell therapy) in patients with gliomas[7,8].

Due to the disparity of clinical trials evaluating new treatments for high-grade gliomas[9], none of the new immunotherapies have been approved for administration as first-line therapy. Thus, the present study aimed to collect and evaluate the available evidence about the efficacy (overall survival and progression-free survival) and safety of active and/or passive immunotherapies for the treatment of adult patients with high-grade gliomas.

METHODS

The present study followed the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[10] and the Cochrane Handbook for Systematic Review and Meta-analyses[11]. The protocol is registered in PROSPERO (registration number CRD42020163253).

Search strategy

Descriptors regarding high-grade gliomas, immunotherapies and clinical trials were combined using the Boolean operators "OR" and "AND". Full search strategies for all databases are presented in Supplementary Table S1 (https://osf.io/nv9ec/). A manual search was also conducted by checking the reference lists of included articles. Systematic searches were conducted in PubMed, Scopus, and Web of Science on December 5, 2020. No restrictions (e.g., year of publication, languages) were applied to the search.

Eligibility criteria

The acronym PICOS (population, intervention, comparator, outcomes, and study design) guided the eligibility criteria definition. Population consisted in adult patients with high-grade gliomas undergoing conventional treatments (surgery, radiotherapy, and chemotherapy), the intervention included active or passive immunotherapies (checkpoint inhibitors, monoclonal antibodies, vaccines, CAR T-cell therapy), the comparators were placebo or active treatments other than immunotherapies, the outcomes comprised efficacy in terms of overall survival (OS) and/or progression-free survival (PFS) and safety as assessed by the occurrence of adverse events, and study design included randomized controlled trials (RCTs). Studies published in non-Roman characters were excluded.

Study selection, data extraction, and quality assessment

Two authors independently performed the study selection, data extraction, and risk of bias assessment. In case of discrepancies, a third reviewer was consulted. The extracted data comprised author information, year of publication, country of study, study design (blinded or open label), patients' characteristics (number of patients in each group, sex, age, Karnofsky overall performance scale (KPS) at baseline, genetic markers (MGMT and IDH), regimen of controls (previous treatment or placebo), and characteristics of the intervention and control (dosage and treatment duration). Risk of bias was assessed for the outcomes OS and PFS by using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2)[12,13].

The quality of evidence for the outcomes OS and PFS was assessed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which considers study design, risk of bias, inconsistency, indirectness and imprecision in the analysis[14].

Statistical analysis

The meta-analysis graphs and funnel plots were obtained by using Review Manager (RevMan) software version 5.4.1. Since most of included studies reported dichotomous outcomes, effect size measures were assessed by using risk ratio (RR) and 95% confidence intervals (CIs). The Mantel-Haenszel method and random effects model were applied.

Heterogeneity was estimated by the I^2 test (I^2 > 50% indicating significant heterogeneity)[15]. To evaluate the effect of each study on the heterogeneity data, sensitivity analyses have been performed, which consisted of the hypothetical and sequential removal of studies from the meta-analysis. No study was permanently removed from the analyses. Publication bias was estimated through visual inspection for symmetry of the funnel plots[16]. In cases where sufficient data were available (at least two studies), subgroup analyses (e.g., type of immunotherapy) were conducted. For meta-analysis with significant statistical difference between groups the prediction interval was calculated[17].

RESULTS

Search results

Through the database search, 6073 articles were identified, of which 5923 had been excluded after title and abstract screening. Of the 150 potentially relevant articles included for full-text assessment, 131 were excluded (87 were not RCTs, 30 did not report the outcomes of interest, five were published in non-Roman characters, four were paediatric studies, two did not provide extractable data, two were excluded because of lack of access and one presented immunotherapy in both arms). The list of studies excluded after full-text assessment is provided in Supplementary Table S2 (https://osf.io/nv9ec/?view_only

=f0e9742525a748dea165f28504ac9b94). No additional study was identified through manual search. Therefore, 19 RCTs had been included in the systematic review, of which 15 reported comparable data for meta-analysis (Figure 1). The most common immunotherapies found in the included studies comprised vaccines.

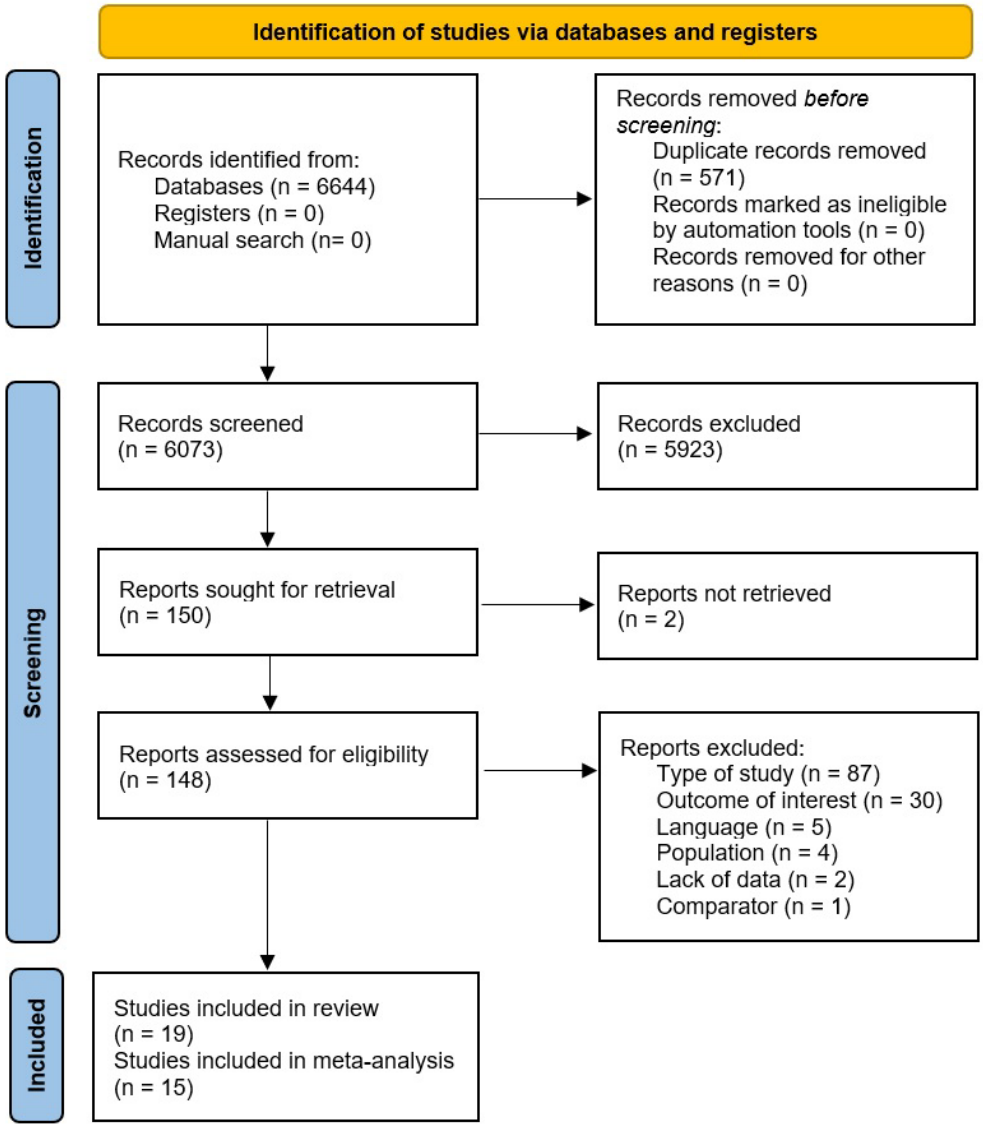

Figure 1. Prisma Flow Diagram - database search and study identification

Study characteristics

Overall, this systematic review included 12 phase II randomised clinical trials, four phase III trials, and three that did not report the study phase, with a total of 2196 patients with recurrent or newly identified high-grade gliomas who underwent traditional treatments. The main characteristics of the included RCTs are summarised in Table 1. Included studies were published between 1973 and 2020. Thirteen RCTs were multicentre studies[21,23-29,32-35,37], two were conducted in China[22,31], two in the United States[19,36], one in Japan[20], and one in the United Kingdom (London)[18].

Table 1. Characteristics of the included studies.

Author	Year	Country	N total	N men	Study design	Intervention	Control	Premedication	Diagnosis	Treatment duration	IDH1/2 status	MGMT
Bloom et al.[18]	1973	London	62	45	RCT	Autologous cells	Surgery and RT	Surgery and RT	Histological grade III/IV	-	No	No
Fischer et al.[19]	1985	USA	25	13	RTC	RT with levamisole	RT alone	Surgery	Pathological diagnosis of GBM multiforme	Until disease progression	No	No
Shibata et al.[20]	1987	Japan	51	26	RTC	Radioimmunochemotherapy ACNU plus picibanil (OK-432)	Radiochemotherapy with ACNU only	Surgery and RT	Supratentorial GBM and malignant astrocytomas	-	No	No
Bogdahn et al.[21]	2011	Multicentre	134	87	RTC/open label	Trabedersen (AP 12009)	Standard chemotherapy (TMZ/PCV)	Surgery, RT, and chemotherapy	Neuropathology -confirmed diagnosis of recurrent/refractory AA or GBM	Until disease progression	No	No
Cho et al.[22]	2012	China	34	16	RCT	Adjuvant autologous DC-based vaccine	Conventional treatment	Surgery and RT with concomitant and adjuvant TMZ chemotherapy	Histologically confirmed (WHO) IV gliomas	Until disease progression	No	Yes
Solomón et al.[23]	2013	Multicentre (Cuba)	70	30	RTC/DB	Radiotherapy plus nimotuzumab	Placebo and RT	Surgery	Previously stratified by histology (GBM vs. AA)	Until 1 year	No	No
Wick et al.[24]	2014	Multicentre	72	51	RTC/open label	rRT plus APG101	Second radiotherapy (rRT)	Surgery, RT, and chemotherapy	First or second progression of a histologically confirmed GBM	Until progression	Yes	Yes
Westphal et al.[25]	2015	Multicentre	142	87	RTC/open label	Nimotuzumab plus TMZ combined with radiation	TMZ plus radiation	Surgery	Histologically confirmed GBM (WHO 2007)	Until progression	No	Yes
Ursu et al.[26]	2017	Multicentre (France)	81	48	RTC/SB	CpG-28 plus SOC	SOC treatment (RT and concomitant TMZ)	-	MRI suggestive of GBM	-	Yes	Yes
Kong et al.[27]	2017	Multicentre (Korea)	180	102	RTC/open label	CIK cells combined with standard TMZ	Standard TMZ chemoradiotherapy alone	Surgery and RT	Newly diagnosed GBM (WHO) grade IV astrocytoma	-	No	No
Weller et al.[28]	2017	Multicentre (22 countries)	745	480	RCT/DB	Rindopepimut plus TMZ	Control plus TMZ	Surgery and RT with concomitant and adjuvant TMZ chemotherapy	Confirmation of GBM histology	Until disease progression	No	Yes
Bota et al.[29]	2018	Multicentre (USA)	9	7	RCT/DB	ERC1671 vaccine	Placebo	Surgery and RT with concomitant and adjuvant TMZ chemotherapy	Histologically confirmed grade IV malignant glioma	-	Yes	Yes
van den bent et al.[30]	2019	Multicentre	155	102	RTC/open label	Bevacizumab in combination with TMZ	TMZ alone	Surgery, RT, and chemotherapy	Locally diagnosed grade II or III glioma (WHO 2007)	Until progression	Yes	Yes
Yao et al.[31]	2019	China	43	24	RTC/DB	GSC-DCV	Placebo	Surgery, RT, and chemotherapy	New or recurrent GBM	Until disease progression	Yes	Yes
Buchroithner et al.[32]	2019	Multicentre (Austria)	76	51	RTC/ open label	SOC plus vaccination with autologous DCs (Audencel)	SOC	Surgery	Histologically proven primary GBM	-	Yes	Yes

Table 1. Continued...

Author	Year	Country	N total	N men	Study design	Intervention	Control	Premedication	Diagnosis	Treatment duration	IDH1/2 status	MGMT
Narita et al.[33]	2019	Multicentre (Japan)	88	56	RCT/DB	Personalised peptide vaccination (PPV)	Placebo plus BSC	Standard TMZ and radiotherapy	Supratentorial rGBM that had been diagnosed histologically	Until disease progression	No	No
Cloughesy et al.[34]	2019	Multicentre	32	12	RTC/ open label	Neoadjuvant pembrolizumab	Adjuvant-only group	Surgery and RT	Recurrent GBM	Until tumour progression	Yes	Yes
Wen et al.[35]	2019	Multicentre	124	75	RTC/DB	ICT-107 (pulsed DCs)	Placebo and adjuvant TMZ	Surgery and radiochemotherapy	Histologically confirmed GBM	Until disease progression	No	Yes
Reardon et al.[36]	2020	26 hospitals in (USA)	73	41	RTC/DB	Rindopepimut + bevacizumab	Control plus bevacizumab	Maximum feasible resection or biopsy, radiation, and TMZ	First or second relapse of histologically confirmed GBM	Until progression	No	No

AA, anaplastic astrocytoma; ACNU, nimustine hydrochloride; BSB, best supportive care; DC, dendritic cell; DB, double blind; GBM, glioblastoma; IDH, isocitrate dehydrogenase; MGMT, O-6-methylguanine-DNA methyltransferase; PCV, vincristine; RCT, randomised clinical trial; RT, radiotherapy; SB, single blind; SOC, Standard of care; TZM, temozolomide; WHO, World Health Organization.

The sample size of the included studies ranged from 9 to 745 participants, with more males (62%) than females. The interventions assessed in the present systematic review comprised specific immunotherapies, which were categorised as follows: (a) active immunotherapy in 13 studies (four used dendritic cell [DC] vaccination[22,31,32,35], three used peptide vaccination[28,33,36]; three used non-specific antigen vaccines[19,20,26], and three applied autologous tumour cell therapy[18,27,29]); and (b) passive immunotherapy in six studies (five used antibody-based immunisation[23-25,34,37] and one employed the antisense oligonucleotide trabedersen[21]). Eight studies did not provide information on the genetic markers (IDH1/2 status and MGMT mutation) used for classification, diagnosis, and/or treatment[18-21,23,27,33,36]. In most studies, the duration of treatment extended until disease progression.

Efficacy results

Efficacy assessment comprised the outcomes OS and PFS at 6 months, at 12 months, and at more than 12 months. Fifteen studies were included in the meta-analyses, of which thirteen[19-23,25-28,30,33,35,36] comprised OS analysis (Figure 2) and nine[23-27,30,32,35,36] the PFS analysis (Figure 3).

For both meta-analyses no statistical differences were observed among immunotherapy and traditional treatment, except for OS at more than 12 months, for which statistical difference favouring immunotherapy was observed (RR 1.13, 95% CI [1.01, 1.27], p = 0.04). Nevertheless, the calculated prediction interval for this outcome ranged from 0.97 to 1.29, revealing that with the inclusion of future studies in the analysis this statistical difference may not be observed. In both meta-analyses (for the OS and the PFS outcomes), heterogeneity was low.

Subgroup analyses were conducted for the outcome OS at more than 12 months, grouped by active and passive immunotherapies. No statistical differences were observed between the compared groups. Forest plots of these analyses are presented in the Supplementary Figures S1 and S2 (https://osf.io/nv9ec/?view_only=f0e9742525a748dea165f28504ac9b94).

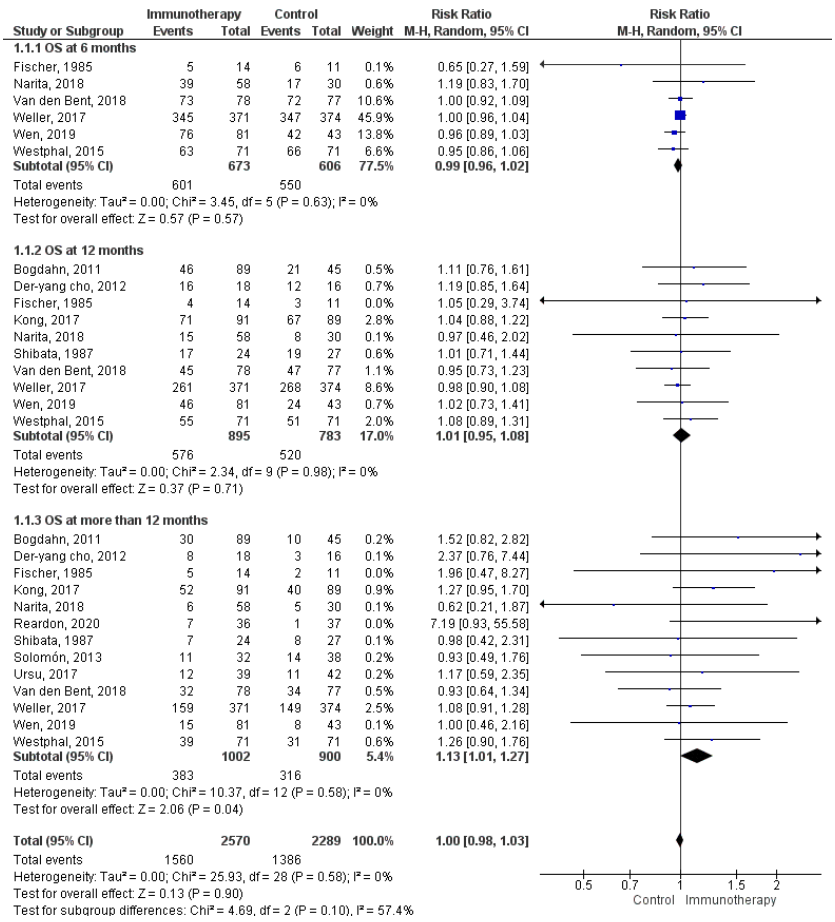

Figure 2. Forest plots for the meta-analyses comparing the efficacy outcomes between immunotherapy and control for high grade glioma; overall survival (OS at 6 months; OS at 12 months and OS at more than months).

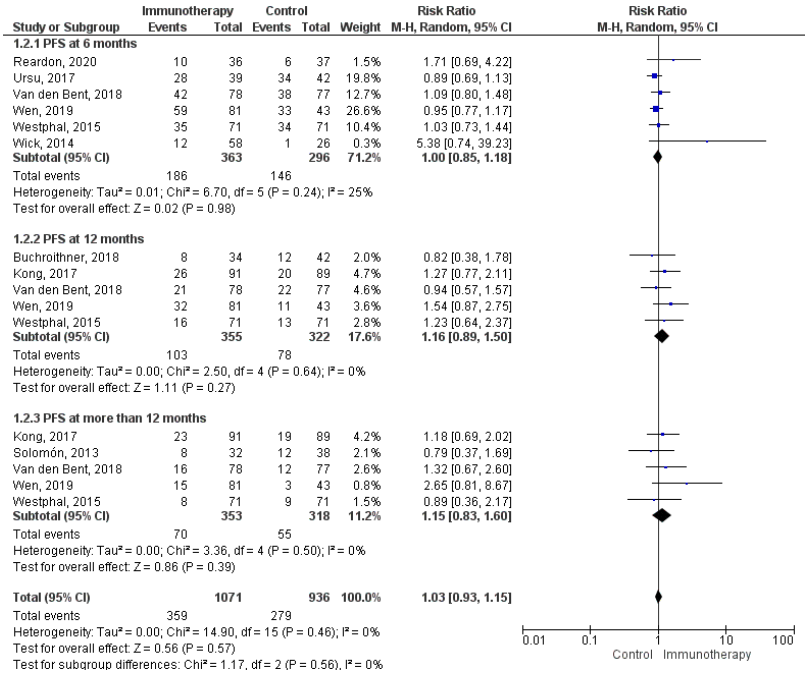

Figure 3. Forest plots for the meta-analyses comparing the efficacy outcomes between immunotherapy and control for high grade glioma; progression-free survival (PFS at 6 months; PFS at 12 months and PFS at more than months).

Safety results

Due to the lack of comparability between studies reporting adverse events (AEs), it was not feasible to perform a meta-analysis for safety outcomes. Therefore, the outcomes are presented in a narrative way.

The main AEs reported in the included studies comprised nervous system disorders (headache, cerebral oedema, convulsion, dizziness, insomnia, depression, and anxiety), haematologic disorders (thrombocytopenia), gastrointestinal disorders (nausea and vomiting, diarrhoea, or constipation), injection site reaction, fatigue, and infection, as summarised in Table 2. Deaths from AEs were rare, and the rate of treatment-related demise between immunotherapy and control arms were similar. In the study performed by Weller et al.[28], all sixteen deaths reported were due to adverse events (nine [4%] in the rindopepimut group and seven [3%] in the control group), and a pulmonary embolism in a 64-year-old male patient after eleven months of treatment was considered to be potentially associated with rindopepimut immunotherapy.

Table 2. Main adverse effects (AEs) reported.

	Control					Immunotherapy				
Author/year	**N total events**	**Treatment discontinuation due to AEs**	**Deaths due to AEs**	**Principal specific AEs**	**AEs ≥ grade 3**	**N total events**	**Treatment discontinuation due to AEs**	**Deaths due to AEs**	**Principal specific AEs**	**AEs ≥ grade 3**
Bloom **et al.**[18] (1973)	-	-	-	-	-	6	-	-	Injection site skin reactions (6/35) #	-
Fischer **et al.**[19] (1985)	-	-	-	-	-	-	4	2	Vomiting Confusion	-
Shibata **et al.**[20] (1987)	-	-	-	-	-	-	-	-	Severe leukopenia	-
Bogdahn **et al.**[20] (2011)	-	22%	-	Nervous system disorders	Cerebral disorder	-	46% (10 µM) e 49% (80 µM)	-	Nervous system disorders	Meningitis, hyponatremia, brain edema, thrombocytopenia
Cho **et al.**[22] (2012)	-	2	-	A scalp infection (1/16) # Nausea and vomiting (2/16) #	-	-	-	-	Transient abnormal liver function (1/18) # Mild lymphopenia (1/18) #	-
Solomón **et al.**[23] (2013)	-	-	-	Headache, seizures, dry radiodermitis, fever, asthenia, alopecia and alteration of the liver function tests	-	-	-	-	Nausea, tremors, anorexia, increase of the liver function parameters and fever	-
Wick **et al.**[24] (2014)	-	3	-	-	Nervous system disorders	-	-	-	-	Nervous system disorders
Westphal **et al.**[25] (2015)	-	-	-	Headache (34/71) # Fatigue (31/71) # Nausea (23/71) # Vomiting (20/71) #	6 events	-	-	-	Headache (38/71) # Fatigue (39/71) # Nausea (32/71) # Vomiting (24/71) #	22 events
Ursu et. al. [26] (2017)	-	-	-	Septic shock, generalised seizure and fever	3	-	-	1	Epileptic seizures, grade IV thrombopenia, pancytopenia, grade IV lymphopenia	7
Kong **et al.**[27] (2017)	-	4	-	-	-	-	6	-	-	Neutropenia, pneumonia, acute renal failure
Weller **et al.**[28] (2017)	-	-	7	Thrombocytopenia (23/372) #	Seizure (22/372) # Brain edema (12/372) #	-	8	9	Thrombocytopenia (32/369) #	Seizure (18/369) # Brain edema (7/369) #

Table 2. Continued...

Author/year	Control					Immunotherapy				
	N total events	Treatment discontinuation due to AEs	Deaths due to AEs	Principal specific AEs	AEs ≥ grade 3	N total events	Treatment discontinuation due to AEs	Deaths due to AEs	Principal specific AEs	AEs ≥ grade 3
Bota **et al.**[29] (2018)	58	-	-	Gait disturbance/fall (38/57) *	8	162	-	-	Arthralgia (70/59) * Injection site reactions (67/59) *	4
van den Bent **et al.**[30] (2018)	-	-	-	Nervous system disorders (59/75) # Fatigue (53/75) # Nausea (39/75) # Infections (17/75) #	8	-	-	1	Nervous system disorders (65/76) # Fatigue (61/76) # Nausea (43/76) # Infections (29/76) #	39
Yao **et al.**[31] (2018)	-	-	-	-	-	2	-	-	A mild fever (1/22) # Erythema at the vaccine injection site (1/22) #	-
Buchroithner **et al.**[32] (2018)	-	-	-	Severe thrombocytopenia	-	-	-	-	Local pain and local reactions (6/34) #	-
Narita **et al.**[33] (2018)	120	-	-	Injection site skin reactions (18/16) *	11	340	-	-	Injection site skin reactions (45/41) *	23
Cloughesy **et al.**[34] (2019)	-	-	-	-	-	-	2	-	-	2
Wen **et al.**[35] (2019)	-	-	-	Fatigue (11/43) # Convulsions (11/43) # Nausea (4/43) #	-	-	-	-	Fatigue (12/80) #; Convulsions (7/80) # Nausea (6/80) #	-
Reardon **et al.**[36] (2020)	-	-	-	Brain edema (8%)	-	-	-	-	Brain edema (3%)	-

(*) Number of events/number of patients; (#) Number of patients who had an adverse effect/total number of patients.

Quality of the studies

Risk of bias assessment of the fifteen studies included in the meta-analyses is detailed in Figure 4. The evaluation was conducted for the outcomes OS and PFS revealing a high overall risk of bias in six assessments, low in eight and some concerns in eight estimates. The absence of a detailed explanation regarding the randomization process and allocation concealment (first domain of the risk of bias tool), along with the open-label nature of some studies, contributed to the high overall risk of bias detected. The full risk of bias analysis with justifications is provided in the supplementary material (Supplementary table S3 [https://osf.io/nv9ec/?view_only=f0e9742525a748dea165f28504ac9b94]).

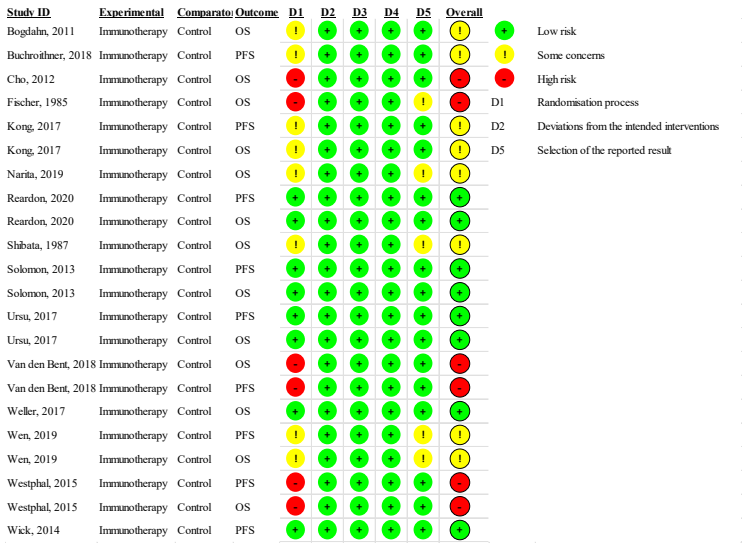

Figure 4. Risk of bias assessment of the studies included in the meta-analyses

Publication bias

Funnel plots for OS and PFS meta-analyses are presented in Figures 5A and B, respectively. These graphs show symmetry on visual inspection, indicating no publication bias.

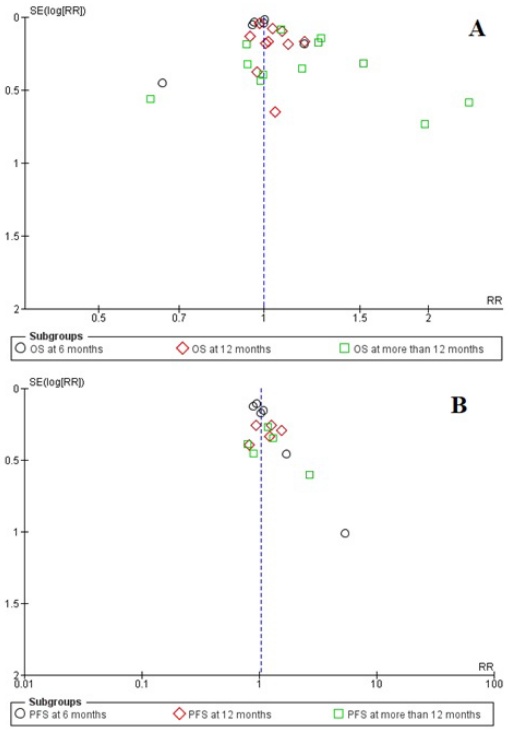

Figure 5. Funnel plots for the meta-analyses; A, overall survival; B, progression-free survival; the funnel plots were constructed as scatter plots in which the treatment effects estimated from individual studies (HRs or ORs) on the horizontal axis are plotted against a measure of study precision (SE of log [HR] or SE of log [OR]) on the vertical axis. The plot resembles a symmetrical inverted funnel because the estimates of the treatment effect from smaller studies are scattered more widely at the bottom of the graph, with the spread narrowing with increasing precision among larger studies, which indicated no significant publication bias.

Quality of evidence

The quality of evidence assessment, according to GRADE approach, was conducted for the outcomes OS and PFS (Figure 6). Both outcomes were considered as critical and the certainty regarding both analyses was moderate. For both assessments serious risk of bias was observed, which downgraded the quality of evidence.

Certainty assessment							№ of patients		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imunotherapy	Control		
Overall survival										
13	randomised trials	serious[a]	not serious	not serious	not serious	none	1560/2570 (60.7%)	1386/2289 (60.6%)	⊕⊕⊕◯ Moderate	CRITICAL
Progression-free survival										
9	randomised trials	serious[b]	not serious	not serious	not serious	none	359/1071 (33.5%)	279/936 (29.8%)	⊕⊕⊕◯ Moderate	CRITICAL

Explanations

a. Of the 13 included studies, 4 presented a high overall risk of bias according to RoB 2 tool.

b. Of the 9 included studies, 2 presented a high overall risk of bias according to RoB 2 tool.

Figure 6. Quality of evidence assessment.

DISCUSSION

Although defined as promising for the treatment of high-grade gliomas[38], immunotherapies were not superior to conventional treatment (chemotherapy, radiotherapy, and surgery) in the present meta-analyses. A statistical difference was observed in favour of immunotherapies for the outcome OS at more than 12 months; however, the diamond was close to the null line, and the studies included in this analysis had large confidence intervals, indicating that caution should be taken when interpreting this result. When the prediction interval was calculated for this analysis[17], no statistical difference was observed. Additionally, we conducted subgroup analyses for this outcome by immunotherapy type, which also showed that immunotherapies were no superior to conventional treatment. Regarding the risk of bias of included studies, four presented a high overall risk, due to the absence of a detailed explanation about the randomization process and allocation concealment. Future studies should be better planned and better reported, in order to improve the quality of the available evidence.

With the improvements in immune-mediated anticancer treatment options in the last decade, such as in the field of gliomas, state-of-the-art techniques had been efficiently applied in preclinical models. However, clinical trials did not produce consistent outcomes. This suggests that knowledge about the infiltration of complex immune cells and their interaction with tumour cells is still limited, as well as the timing of treatment, the combination of immunotherapy with different therapies, and the course of agent administration. Thus, applying those immunotherapeutic modalities to treat malignant glioma is still challenging, and investigations about combination therapies are still needed[39].

According to Lim et al.[6], the reasons why tumours do not respond to immunotherapy are likely multifactorial, including a distinctly immunosuppressive tumour environment, defects in tumour antigen presentation, and functions of the physical microenvironment, which includes hypoxia and necrosis. Therefore, the authors recommended that rationally planned strategies are crucial for the improvement of effective treatment strategies. As discussed by van Gool et al.[40], despite numerous meta-analyses on immunotherapy treatment for GBM have suggested a significant increase in OS, no studies group has been able to expose the efficacy of this form of treatment in a prospective study due to the complexity of tumour biology and tumour-host interactions that prevent adequate stratification of a control group. Therefore, the authors suggest that individualised drugs, consisting of multimodal immunotherapies, may be an excellent method to acquire long-time period tumour control. However, novel strategies should be considered in the assessment of the efficacy of complex, customized therapies.

A previous systematic review with meta-analysis included 25 studies assessing patients with gliomas treated with specific immunotherapy and evaluated OS and PFS at 6 months, 12 months, and more than 12 months. Overall, the mean OS was not statistically significant in the immunotherapy group (median difference = 1.51; 95% CI [-0.16, -3.17]; p = 0.08), corroborating the results of our analyses. On the other hand, it is important to note that the 12-month OS was significantly higher withinside the immunotherapy groups (HR = 0.69; 95% CI [0.52, 0.92]; p = 0.01), and the median PFS was considerably higher in the immunotherapy group[8]. Our meta-analysis did not reveal significant advantages of immunotherapies. A possible explanation for the observed disparities in the efficacy results is the fact that we included studies assessing adult patients only, in order to analyse a more homogeneous population.

Although vaccination with dendritic cells (DCs) is considered an important step in most cancers' treatment, some of the outcomes published over time have not been consistent, creating uncertainty in clinical decision-making. Artene et al. performed a meta-analysis on therapy with DCs and confirmed that vaccination with this therapy improves the OS for newly diagnosed and recurrent high-grade gliomas when compared to conventional treatment, and the improvement in PFS was not statistically significant for newly diagnosed patients[38,41]. Li et al., in a meta-analysis evaluating the efficacy of DCs in treating high-grade gliomas,

particularly in terms of OS, PFS, and adverse effects, concluded that the DC vaccine can significantly improve OS and PFS with acceptable toxicity; however, further studies should be conducted to confirm these results[42]. In a review by Lv et al., when compared to the placebo control group the DC vaccine was related to significantly progressed OS in glioblastoma patients (HR 0.69, 95% CI [0.49, 0.97], p = 0.03). In addition, a trend towards improved PFS was detected in patients allocated to the DC vaccine group in comparison to the ones in the control group (HR 0.76, 95% CI [0.56, 1.02], p = 0.07)[43].

Regarding safety data, a study by Magee et al. that profiled adverse events from immunotherapy agents in comparison to chemotherapy in solid organ tumours confirmed that patients receiving immunotherapy agents were much less likely to develop severe AEs (≥grade 3) compared to the ones receiving standard chemotherapy regimens. Patients receiving immunotherapy were additionally much less probably to develop an AE of any grade, terminate therapy, or die from a treatment-associated AE. Nonspecific symptoms, fatigue and diarrhoea were additionally less likely to occur in the immunotherapy group as compared to patients receiving chemotherapy. Therefore, despite our difficulty in comparing the adverse events extracted data, safety outcomes reported individually by the authors of the eligible studies are in line with the findings of the cited review[44].

In view of the inconsistencies between clinical trials regarding the benefits of immunotherapies for the treatment of patients with high-grade gliomas, is paramount to assess the quality of the evidence generated by systematic reviews with meta-analysis synthesizing the results from these trials. In this sense, we conducted the quality of evidence assessment according to GRADE approach, which revealed that the certainty on the current evidence concerning immunotherapies for high-grade gliomas treatment is moderate, particularly due to the high overall risk of bias observed in some of the included studies. Hence, further high-quality clinical trials evaluating these therapies are needed in order to provide conclusive evidence and strong recommendations towards the use of immunotherapies in clinical practice.

Limitations

As with any systematic review, our study has a few limitations. First, information about the endpoints (OS or PFS), previous treatment history, treatment duration, and adverse effects was not available in all studies, although some of the included studies justified such limitations. Secondly, five studies published in non-Roman characters were ineligible for inclusion, as well as two studies due to lack of access. Finally, we performed subgroup analyses that were not specified in the original review protocol. Despite these limitations, the strengths of this meta-analysis include the strict methodological inclusion standards that required comparison among an immunotherapy group and a standard treatment group and a rigorous, updated search strategy. In addition, we evaluated the quality of evidence according to GRADE approach, revealing the certainty on the current available evidence.

CONCLUSION

This is the most comprehensive meta-analysis assessing the efficacy of immunotherapies compared to standard treatments in adult patients with high-grade gliomas. Overall, no evidence of an additional benefit of immunotherapies in comparison to standard treatment was observed. Since the certainty on the current available evidence is moderato further high-quality clinical trials evaluating these therapies are needed. In addition, we suggest that systematic reviews assessing observational studies should be conducted to verify whether this result is consistent with evidence from real world studies.

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Authors' contributions

E.T.S., H.H.L.B., and R.P. designed the study; H.H.L.B. and R.P. planned the statistical analyses: E.T.S. and H.H.L.B. performed the key analyses; E.T.S. and H.H.L.B. generated and collected the data; E.T.S., F.F.M., and I.M.P. assisted in data interpretation; E.T.S. wrote the manuscript; H.H.L.B., A.W. and R.P. revised the manuscript.