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REVIEW

Optimal treatment strategy for adult patients with newly diagnosed glioblastoma: a systematic review and network meta-analysis

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Abstract

To compare the efficacy and safety of treatments based on the Stupp protocol for adult patients with newly diagnosed glioblastoma and to determine the optimal treatment option for patients with different O-6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation statuses. We estimated hazard ratios (HRs) for overall survival (OS) and odds ratios (ORs) for adverse events of grade 3 or higher (AEs ≥ 3). Twenty-one randomized controlled trials involving 6478 patients treated with 21 different treatment strategies were included. Results of the pooled HRs indicated tumor-treating fields (TTF) combined with the Stupp protocol resulted in the most favorable OS for patients with and without *MGMT* promoter methylation. Subgroup analyses by the two *MGMT* promoter statuses indicated that lomustinetemozolomide plus radiotherapy or TTF combination therapy was associated with the best OS for patients with methylated *MGMT* promoter (HR, 1.03; 95% credible interval [CI], 0.54–1.97), and standard cilengitide combination therapy or TTF combination treatment was associated with the best OS for patients with unmethylated *MGMT* promoter (HR, 1.05; 95% CI, 0.67–1.64). Regarding AEs ≥ 3, there were no significant differences in pooled ORs. However, Bayesian ranking profiles that demonstrated intensive cilengitide combination therapy and TTF combination therapy have a similar possibility to cause the least toxicity. These results indicated that TTF combination therapy was associated with increased survival, irrespective of the *MGMT* promoter methylation status, and a relatively tolerated safety profile compared with other combination treatments. The optimal treatment option for glioblastoma patients with different *MGMT* promoter methylation statuses was different.

Keywords Glioblastoma · Meta-analysis · Overall survival · Toxicity · Treatment

Introduction

Glioblastoma (GBM) is the most frequent and aggressive primary central nervous system tumor in adults. Although the Stupp protocol, improving the survival from an average of 10 months to 14 months, has been widely established as the standard therapy for adult patients with newly diagnosed GBM, the prognosis for this population remains relatively poor [1]. Standard therapy consists of maximal safe surgical resection or a diagnostic biopsy, followed by concurrent chemoradiotherapy and then maintenance chemotherapy for six cycles, where chemotherapy is comprised of temozolomide [2]. Since then, multiple combination treatments based on the Stupp protocol were compared with standard therapy by head-to-head randomized controlled trials (RCTs). Especially, the trial NCT00916409 [3] and the trial NCT01149109 [4] showed meaningful results. Beyond that, different schemes of adjusted temozolomide use in maintenance chemotherapy were also tested.

The relative efficacy and safety relation between any two therapy strategies from available RCTs and the optimal

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treatment option for adult patients with newly diagnosed GBM remain unclear. Furthermore, a previous study indicated that the methylation status of the O-6-methylguanine-DNA methyltransferase (*MGMT*) promoter influences the prognosis of GBM patients who receive alkylating agents [5], but it remains unclear whether the ideal treatment differs in patients with different *MGMT* promoter methylation statuses. Published RCTs and pairwise meta-analyses only using the direct comparison model were performed to collect evidence about the comparative efficacy and safety between the experiment arm and the Stupp protocol. They both failed to address the aforesaid problems.

In contrast, network meta-analysis could determine the optimal treatment option and elucidate the relative relation among available treatments by synthesizing evidence from direct and indirect comparisons. A prior network meta-analysis [6] neither included recently published trials nor considered different subtypes in patients with GBM. We performed this network meta-analysis of randomized controlled trials to investigate the relative efficacy and safety of treatments based on the Stupp protocol in adult patients with newly diagnosed GBM to identify the optimal option. Moreover, subgroup analysis was performed to investigate whether the ideal choice would be changed depending on the MGMT promoter methylation status (including methylated and unmethylated promoters).

Methods

This network meta-analysis was designed and performed following the preferred reporting items for systematic reviews and meta-analyses and its extension statement for network meta-analyses [7]. The protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO CRD42020157020).

Literature search

PubMed, Embase, and the Cochrane Central Register of Controlled Trials databases were inspected using the algorithm "(glioblastoma OR GBM) NOT ("recurrent glioblastoma" OR "recurrent GBM")" until November 5, 2019, as we started the literature retrieval on this day. Only English publications were included. Moreover, only RCTs were included to select for specific population and study characteristics, to ensure that the sets of studies were comparable and indirect estimates were valid. Besides, we manually searched the trial registries of ClinicalTrials.gov for unpublished eligible trials.

Study selection and eligibility criteria

We only included phase II/III RCTs published in English that met the following criteria: (i) trials included patients aged ≥ 18 years with newly diagnosed and pathologically confirmed GBM (World Health Organization grade IV astrocytoma) [8]; (ii) trials included at least one intervention following the Stupp protocol or an adjusted Stupp protocol (only involving adjustments of temozolomide dose during maintenance chemotherapy); (iii) trials reported at least one of the following clinical outcome measures: (a) overall survival (OS), defined as the time from randomization until death from any cause; (b) toxicity regarding adverse events (AEs) of grade 3 or higher (AEs ≥ 3), which were defined and graded by the National Cancer Institute Common Toxicity Criteria for AEs.

Exclusion criteria were the following: (i) noncomparative RCTs, which could not sufficiently detect the difference between the reference and the experimental arm [9]; (ii) trials investigating patients with high-grade glioma but not restricted to GBM; (iii) patients only undergoing biopsy diagnosis but not surgical resection; (iv) patients were all defined as elderly people; (v) trials in which adjusting temozolomide use was aimed at other phases than the maintenance chemotherapy phase. Criteria (ii)–(v) were applied because if these criteria are not met, this might introduce bias due to the heterogeneity of patient characteristics.

Titles and abstracts of relevant studies were screened, and then, ineligible studies were excluded by assessing the full text for final analysis. Also, the reference lists of the included articles, and prior network meta-analyses were thoroughly checked for potentially eligible articles. Two investigators (LJ and YZM) independently reviewed articles from the above databases on the basis of the aforementioned inclusion and exclusion criteria, and disagreements were resolved in a discussion group.

Data collection process

Two investigators (LJ and YZM) independently reviewed the full texts of eligible studies and extracted information into a spreadsheet, which included first author, publication year, study design, number of patients, baseline characteristics, the *MGMT* promoter methylation status of patients (if available), interventions, the details of temozolomide administration during maintenance chemotherapy, and reported outcomes. Outcome measures from longer follow-up analyses were preferable if provided. When needed data were not reported or published, we contacted the authors of relevant studies. Any divergences were resolved by reaching a consensus after group discussion.

Some studies were found to have some different traits. First, in the Weller study [10], the control group was comprised of the Stupp protocol and the Keyhole limpet hemocyanin, the latter serving to maintain blindness. Considering that the therapeutic effect on the tumor was not likely to be affected by the Keyhole limpet hemocyanin, we assumed that the control group in the Weller study was equivalent to the Stupp protocol control groups in other trials. Furthermore, the extracted statistical results

were based on patients with a minimal residual disease rather than all patients recruited in the Weller study, because the former provided statistical results of patients with different *MGMT* promoter methylation statuses, which could be used for subgroup analysis. Second, in seven trials [10–16], maintenance temozolomide was used over six cycles, which was different from the six cycle use of routine temozolomide. However, previous studies [17, 18] indicated that extending temozolomide use to the maintenance chemotherapy phase did not significantly change the OS. We, therefore, considered those control groups using temozolomide over six cycles in the chemotherapy phase as equal to the Stupp protocol. Third, the time points of randomization between included studies were not consistent. Five trials involved randomization after the concurrent radiochemotherapy, and 16 trials involved randomization before the concurrent radiochemotherapy. Fourth, two trials [12, 19] adjusted the delivery pattern of temozolomide instead of merely prolonging the use of temozolomide. Decreasing the time interval was regarded as the first kind of adjusted Stupp protocol, and reducing the daily dosage with a consecutive use was regarded as the second kind of adjusted Stupp protocol.

Risk of bias and quality of evidence

Two reviewers (LJ and SQG) independently assessed the risk of bias of included RCTs using the Cochrane Risk of Bias Tool [20], which is comprised of random sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. Items were classified as low, high, or unclear risk of bias. A funnel plot was used to assess the publication bias and small-scale study effects. Moreover, we used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to evaluate the quality of evidence, in which evaluation items included risk of bias, inconsistency, indirectness, imprecision, incoherence, and transitivity [21, 22].

Statistical analysis

We synthesized all direct and indirect evidence to compare different treatments in terms of efficacy and safety. Efficacy outcome measures were hazard ratios (HRs) for OS, and the safety outcome measures were odds ratios (ORs) for AEs ≥ 3, along with their corresponding 95% credible intervals (CIs). For trials only providing the Kaplan-Meier curves without reporting the HR of OS, the Kaplan-Meier curves were digitized using Engauge Digitizer (www.digitizer.sourceforge.net), and HRs were calculated in R (version 3.6.3) [23]. We only focused on grade 3–4 toxic effects, because grades 1–2 have less clinical significance and were not consistently reported in the included trials. We generated network plots for different outcomes by Stata (version 13.0) to illustrate the geometries about direct or indirect comparison relations in included treatment strategies [24]. For multiple trials performing the same head-to-head comparison, a frequentist, fixed effects, pairwise meta-analysis was used to assess the heterogeneity between relevant studies. The Q test and I^2 were used to estimate the magnitude of heterogeneity; heterogeneity was considered low, moderate, or high for estimated I^2 values under 25%, between 25% and 50%, and over 50%, respectively [25]. Statistical significance was defined as $P < 0.05$. We performed a network meta-analysis using a Markov Chain Monte Carlo simulation technique in OpenBUGS (version 3.2.3) in a Bayesian framework. The fixed effects consistency model was applied because most direct evidence was from one trial. We used non-informative uniform and normal prior distributions and three different sets of initial values to fit the model [26]. Results of the network meta-analysis were outputted as HR, OR, and the corresponding 95% CIs. On the premise of minimally informative priors, CIs can be explained like conventional confidence intervals. Within the Bayesian framework, the surface under the cumulative ranking curve represented the overall ranking of each treatment of the network meta-analysis, where 1 and 0 respectively mean that the treatment is certain to be the best and the worst [27].

Several sensitivity analyses were performed to assess the robustness of results due to the inherent disparity between included studies. The first analysis excluded six studies to eliminate the artificially inevitable bias caused by extracting efficacy outcome measures from Kaplan-Meier survival curves. The second analysis excluded seven studies for the sake of checking the effect of the assumption regarding maintenance temozolomide use over six cycles being equal to six cycles of routine temozolomide use on the results. The third analysis only included phase III RCTs. The fourth analysis divided all included studies into two groups according to the status of randomization before or after the chemoradiotherapy. Correspondingly, subgroup analyses were also performed in each sensitivity analysis.

Results

Characteristics of included studies

We screened 1646 titles and abstracts and 151 full-text articles. Finally, 21 RCTs with a total of 6478 patients who underwent 21 different treatments were included. The detailed process is presented in Fig. 1. Detailed population characteristics are presented in Table 1.

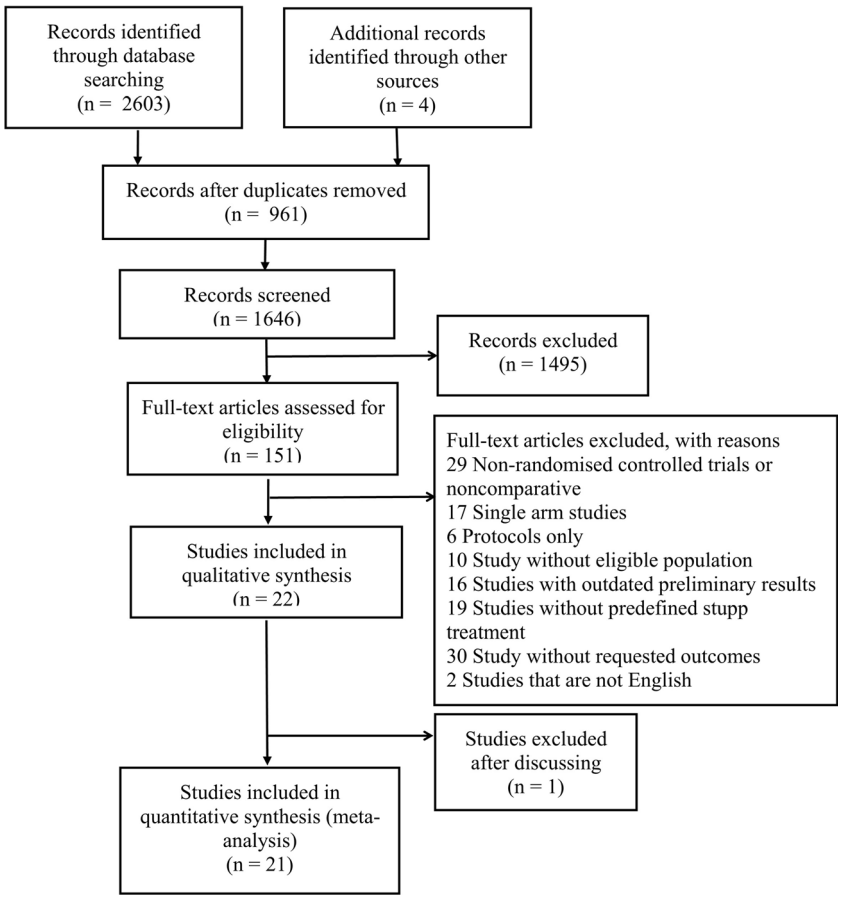

Fig. 1 Flowchart of search results

Results of overall survival

Concerning OS (Fig. 2a), besides lomustinetemozolomide plus radiotherapy (LTR), HRs of other treatments versus tumor-treating fields (TTF) combination therapy were greater than one, and 11 out of 19 treatments had significant differences. Furthermore, LTR showed no different effect when compared with TTF combination treatment (HR, 1.04; 95% CI, 0.58–1.89). In contrast, HRs of other treatments versus everolimus combined with standard therapy were smaller than one, and 12 out of 20 treatments had significant differences. Additionally, no significant difference was observed between the adjusted Stupp protocol and standard therapy (second kind of adjusted Stupp protocol versus the first kind of adjusted Stupp protocol; HR, 1.18; 95% CI, 0.69–2.03; the Stupp protocol versus the first kind of adjusted Stupp protocol; HR, 1.14; 95% CI, 0.69–1.93; and the Stupp protocol versus the second kind of adjusted Stupp protocol; HR, 0.97; 95% CI, 0.83–1.14). Significant outcomes are shown in red and underlined.

Results of AEs ≥ 3

Concerning AEs ≥ 3 (Fig. 2d), some trials only provided the incidence for each specific AEs but not the overall occurrence rate of AEs ≥ 3; those trials were therefore omitted from safety comparisons. Based on 11 available safety comparisons, there was no difference between pooled ORs. ORs of Stupp protocol alone versus each combination treatment were smaller than one. Moreover, we found that ORs of each treatment versus everolimus combination therapy were smaller than one. Besides the Stupp protocol, ORs of each treatment versus TTF combination therapy were greater than one.

Results of subgroup analysis

The Gilbert study [11] could not be used for subgroup analysis because the specific patient numbers of different *MGMT* statuses were not reported. Figure 2 b and c show the relative efficacy between comparable treatments in patients with methylated and unmethylated *MGMT* promoter, respectively. Significant outcomes are shown in red and underlined. In patients with methylated *MGMT* promoter, HRs of other treatments versus LTR were greater than one. TTF combination treatment showed no different effect when compared with LTR (HR, 1.03; 95% CI, 0.54–1.97). In patients with unmethylated *MGMT*, HRs of other treatments versus TTF combination therapy were greater than one. Standard cilengitide combined with standard therapy was found to have

Table 1 Data are expressed as intervention/control unless indicated otherwise. * represents study needs extracting overall survival and corresponding credible interval from Kaplan-Meier curves. § represents study in which temozolomide use on maintenance chemotherapy was over 6 cycles. Total means overall survival results from all patients in trials.

Study (first author, publication year, phase)	Sample size (no)	Median age (years)	Male (%)	Only biopsy (%)	Methylated MGMT (no)
Herrlinger [4], 2019, III	66/63	56/59	71/48	5/2	66/63
Weller [10]§, 2017, III	195/210	59/57	68/58	0/0	69/73
Gilbert [11]§, 2014, III	312/309	NG	57/63	0/0	90/85
Gilbert [12]§, 2013, III	422/411	NG	56/58	3/3	123/122
Stupp [13]§, 2017, III	466/229	56/57	68/69	13/13	137/77
Wen [14]*§, 2019, II	81/43	59/59.8	54.3/72.1	0/0	NG
Wakabayashi [15]§, 2018, II	59/63	61/61	59/60	NG	NG
Chinnaiyan [16]§, 2018, II	88/83	NG	64/55	1/1	NG
Athanassiou [19]*, 2005, II	57/53	NG	63/64	42.1/41.5	NG
Westphal [28], 2015, III	71/71	53/56	59/63	56.3/57.7	15/16
Stupp [29], 2014, III	272/273	58/58	54/52	3/3	272/273
Ursu [30], 2017, II	39/42	62/59	62/57	0/0	10/13
Ursu [31]*, 2019, III	37/38	58/59	56.8/60.5	43.2/44.7	12/21
Stupp [32]*, 2009, III	287/286	56/57	64/61	17/16	46/46
Mallick [33]*, 2018, II	45/38	NG	52/48	0/0	NG
Elinzano [34], 2015, II	42/21	62/62	64/57	0/9.5	0/0
Buchroithner [35]*, 2018, II	34/42	54.6/54	65/69	0/0	NG
Herrlinger [36], 2016, II	116/54	56/56	69/63	0/3.7	0/0
Kong [37], 2017, III	91/89	55/54	56/57	13.2/11.2	NG
Nabors [38], 2015, II	88/89	56/58	57/62	8.0/6.7	0/0
Nabors [38], 2015, II	88/89	56/58	57/62	4.5/6.7	0/0
Chinot [39], 2014, III	458/463	57/56	62/64	13.1/9.5	117/120

Study (first author, publication year, phase)	Unmethylated MGMT (no)	Randomization before/after concurrent chemoradiation	Test arm	Control arm	Reported outcomes
Herrlinger [4], 2019, III	0/0	Before	Lomustine-temozolomide/radiotherapy	S	OS (mMGMT), AE ≥ 3
Weller [10]§, 2017, III	107/119	After	S + rindopepimut	S	OS (total, mMGMT, umMGMT)
Gilbert [11]§, 2014, III	215/214	After	S + bevacizumab	S	OS (total)
Gilbert [12]§, 2013, III	263/254	After	S(2)	S	OS (total, mMGMT, umMGMT), AE ≥ 3
Stupp [13]§, 2017, III	209/95	After	S + TTFields	S	OS (total, mMGMT, umMGMT), AE ≥ 3
Wen [14]*§, 2019, II	NG	After	S + ICT	S	OS (total)
Wakabayashi [15]§, 2018, II	NG	Before	S + interferonβ	S	OS (total)
Chinnaiyan [16]§, 2018, II	NG	Before	S + everolimus	S	OS (total), AE ≥ 3
Athanassiou [19]*, 2005, II	NG	Before	S(1)	RT alone	OS (total)
Westphal [28], 2015, III	33/32	Before	S + nimotuzumab	S	OS (total, mMGMT, umMGMT), AE ≥ 3
Stupp [29], 2014, III	0/0	Before	S + standard cilengitide	S	OS (mMGMT), AE ≥ 3
Ursu [30], 2017, II	25/26	Before	S + CpG-ODN	S	OS (total, mMGMT, umMGMT)
Ursu [31]*, 2019, III	21/13	Before	S + losartan	S	OS (total, mMGMT, umMGMT)

Table 1 (continued)

Stupp [32]*, 2009, III	60/54	Before	S	RT alone	OS (total, mMGMT, umMGMT)
Mallick [33]*, 2018, II	NG	Before	HART/TMZ + TMZ	S	OS (total)
Elinzano [34], 2015, II	42/21	Before	Paclitaxel poliglumex/RT + TMZ	S	OS (umMGMT), AE ≥ 3
Buchroithner [35]*, 2018, II	NG	Before	S + Audencel	S	OS (total)
Herrlinger [36], 2016, II	116/54	Before	Bevacizumab/RT + bevacizumab/irinotecan	S	OS (umMGMT)
Kong [37], 2017, III	NG	Before	S + cytokine-induced killer	S	OS (total), AE ≥ 3
Nabors [38], 2015, II	88/89	Before	S + standard cilengitide	S	OS (umMGMT), AE ≥ 3
Nabors [38], 2015, II	88/89	Before	S + intensive cilengitide	S	OS (umMGMT), AE ≥ 3
Chinot [39], 2014, III	225/236	Before	S + bevacizumab	S	OS (total, mMGMT, umMGMT), AE ≥ 3

MGMT, O-6-methylguanine-DNA methyltransferase; *OS*, overall survival; *AE ≥ 3*, adverse events of grade 3 or higher; *mMGMT*, methylated MGMT; *umMGMT*, unmethylated MGMT; *NG*, not given; *S*, the Stupp protocol consisting of surgical resection followed by concurrent chemoradiotherapy plus maintenance chemotherapy; *TMZ*, temozolomide; *RT*, radiotherapy; *HART*, hypofractionated accelerated radiotherapy; *S(1)*, first kind of adjusted Stupp protocol (150 mg/m^2 on days 1 through 5 and 15 to 19 of a 28-day cycle [up to 6 cycles]); *S(2)*, second kind of adjusted Stupp protocol (75 mg/m^2 for 21 consecutive days of a 28-day cycle [from 6 to 12 cycles]); standard cilengitide (2000 mg 2×/week); intensive cilengitide (2000 mg 5×/week during week 1–6, thereafter 2×/week)

Fig. 2 Pooled estimates of the primary analysis. **a** Pooled hazard ratios (95% credible intervals) for overall survival. **b** Pooled hazard ratios (95% credible intervals) for overall survival on subgroup in patient with methylated MGMT. **c** Pooled hazard ratios (95% credible intervals) for overall survival on subgroup in patient with unmethylated MGMT. **d** Pooled odds ratios (95% credible intervals) for adverse events of grade 3 or higher. Data in each cell are hazard or odds ratios (95% credible intervals) for the comparison of row-defining treatment versus column-defining treatment. Hazard ratios less than 1 and odds ratios more than 1 favor row-defining treatment. Significant results are in red and underscored. LTR, lomustine-temozolomide (six courses)/radiotherapy (first course); S+Cil(1), Stupp + standard cilengitide; BRBI, bevacizumab/radiotherapy + bevacizumab/irinotecan; S+Cil(2), Stupp + intensive cilengitide; PRT, paclitaxel poliglumex/radiotherapy + TMZ; S+Los, Stupp + losartan; S+TTF, Stupp + TTFields; S+Rin, Stupp + rindopepimut; S+CpG, Stupp + CpG-ODN; S+Nim, Stupp + nimotuzumab; S+Bev, Stupp + bevacizumab; S+ICT, Stupp + ICT; S+Aud, Stupp + Audencel; HTT, HART/TMZ+TMZ; S+IFN, Stupp + interferonβ; S+CIK, Stupp + cytokine-induced killer; S+Eve, Stupp + everolimus; S(1), first kind of adjusted Stupp protocol; S(2), second kind of adjusted Stupp protocol; R, radiotherapy; S, Stupp protocol

an effect similar to TTF combination treatment (HR, 1.05; 95% CI, 0.67–1.64).

Results of ranking of treatment strategies

Figure 3 presents the network diagrams of comparisons for efficacy and safety and the Bayesian ranking profiles.

Results of Bayesian ranking were in line with the pooled analyses using HRs and ORs. Concerning OS, LTR was likely to rank first (cumulative probability of 42%). When different *MGMT* promoter statuses were considered, optimal therapies were different. For patients with methylated *MGMT*, LTR was likely to rank the best (33%), and TTF plus standard therapy ranked first for patients with unmethylated *MGMT* (35%). Concerning AEs ≥ 3, everolimus plus standard therapy ranked first (40%), which represented the worst ranking for AEs. In contrast, standard therapy plus intensive cilengitide had the highest probability (20%) of ranking last, followed by TTF combination therapy (18%), which meant that they were associated with the fewest AEs.

Results of heterogeneity, risk of bias, and quality assessments

Forest plots of two pairwise comparisons with respect to heterogeneity estimates (Online Resource Appendix 1) indicated that moderate to high heterogeneity with respect to OS was detected in bevacizumab combined with standard therapy (72.8%) and standard cilengitide combined with standard therapy (71.9%). Minimal heterogeneity (0%) was observed in standard cilengitide combined with standard therapy with respect to AEs ≥ 3. Thirteen RCTs showed a low risk of bias for OS outcomes, while eight RCTs extracting outcomes from Kaplan-Meier curves were associated with an uncertain risk

a

	LTR	S+TTF	S+Eve	S+Bev	S+Nim	S+CIK	S+CpG	S+Cil(1)	S+Cil(2)	S+Rin	S+Aud	S+ICT	S+IFN	S+Los	HTT	PRT	BRBI	S(1)	S(2)	S	R
S+TTF	1.04 (0.58-1.89)																				
S+Eve	2.76 (1.39-5.49)	2.64 (1.71-4.06)																			
S+Bev	1.6 (0.9-2.87)	1.53 (1.23-1.9)	0.58 (0.38-0.88)																		
S+Nim	1.43 (0.71-2.88)	1.36 (0.87-2.13)	0.51 (0.29-0.92)	0.89 (0.58-1.37)																	
S+CIK	1.14 (0.6-2.18)	1.09 (0.76-1.57)	0.41 (0.25-0.69)	0.71 (0.51-1)	0.8 (0.47-1.35)																
S+CpG	1.98 (0.98-4.04)	1.89 (1.19-3.03)	0.72 (0.4-1.3)	1.24 (0.79-1.95)	1.39 (0.76-2.54)	1.73 (1.02-2.97)															
S+Cil(1)	1.5 (0.83-2.73)	1.43 (1.1-1.87)	0.54 (0.35-0.85)	0.93 (0.74-1.18)	1.05 (0.66-1.67)	1.31 (0.9-1.9)	0.75 (0.47-1.22)														
S+Cil(2)	1.42 (0.74-2.74)	1.36 (0.93-1.99)	0.52 (0.31-0.87)	0.89 (0.62-1.27)	1 (0.58-1.71)	1.24 (0.79-1.98)	0.72 (0.41-1.25)	0.95 (0.64-1.4)													
S+Rin	1.67 (0.9-3.11)	1.6 (1.17-2.18)	0.6 (0.38-0.97)	1.04 (0.79-1.38)	1.17 (0.72-1.92)	1.46 (0.97-2.2)	0.84 (0.51-1.4)	1.12 (0.81-1.54)	1.17 (0.77-1.79)												
S+Aud	1.71 (0.78-3.73)	1.63 (0.92-2.9)	0.62 (0.31-1.22)	1.07 (0.61-1.87)	1.2 (0.6-2.38)	1.49 (0.79-2.81)	0.86 (0.43-1.73)	1.14 (0.63-2.04)	1.2 (0.63-2.28)	1.02 (0.56-1.87)											
S+ICT	1.4 (0.66-2.99)	1.34 (0.78-2.29)	0.51 (0.27-0.97)	0.87 (0.52-1.47)	0.98 (0.51-1.89)	1.22 (0.67-2.22)	0.7 (0.36-1.38)	0.93 (0.54-1.61)	0.98 (0.53-1.8)	0.84 (0.47-1.48)	0.82 (0.38-1.74)										
S+IFN	1.65 (0.82-3.38)	1.58 (0.99-2.53)	0.6 (0.33-1.08)	1.03 (0.66-1.62)	1.16 (0.64-2.12)	1.45 (0.85-2.47)	0.83 (0.45-1.54)	1.1 (0.69-1.78)	1.16 (0.67-2.01)	0.99 (0.6-1.64)	0.96 (0.48-1.97)	1.18 (0.6-2.32)									
S+Los	1.89 (0.89-3.99)	1.8 (1.07-3.04)	0.68 (0.36-1.29)	1.17 (0.71-1.95)	1.32 (0.69-2.53)	1.64 (0.92-2.96)	0.95 (0.49-1.84)	1.26 (0.74-2.14)	1.32 (0.73-2.4)	1.13 (0.65-1.96)	1.1 (0.52-2.33)	1.34 (0.65-2.76)	1.13 (0.59-2.2)								
HTT	1.48 (0.53-4.15)	1.42 (0.59-3.41)	0.54 (0.21-1.39)	0.92 (0.39-2.2)	1.04 (0.4-2.7)	1.3 (0.52-3.24)	0.75 (0.28-1.96)	0.99 (0.41-2.39)	1.04 (0.41-2.62)	0.89 (0.36-2.18)	0.86 (0.31-2.42)	1.06 (0.39-2.89)	0.89 (0.34-2.35)	0.78 (0.29-2.12)							
PRT	2.37 (1.01-5.6)	2.27 (1.16-4.43)	0.86 (0.4-1.84)	1.48 (0.77-2.85)	1.66 (0.77-3.59)	2.07 (1-4.26)	1.19 (0.54-2.61)	1.58 (0.8-3.11)	1.66 (0.8-3.45)	1.42 (0.7-2.85)	1.38 (0.59-3.26)	1.69 (0.74-3.88)	1.43 (0.65-3.13)	1.25 (0.55-2.84)	1.58 (0.52-4.77)						
BRBI	1.69 (0.86-3.32)	1.62 (1.07-2.44)	0.61 (0.35-1.06)	1.05 (0.71-1.56)	1.18 (0.67-2.07)	1.48 (0.9-2.41)	0.85 (0.48-1.51)	1.13 (0.74-1.72)	1.18 (0.72-1.96)	1.01 (0.64-1.59)	0.98 (0.5-1.94)	1.2 (0.63-2.29)	1.02 (0.57-1.81)	0.89 (0.48-1.67)	1.12 (0.42-2.98)	0.71 (0.33-1.52)					
S(1)	1.44 (0.68-3.08)	1.38 (0.81-2.35)	0.52 (0.27-0.99)	0.9 (0.54-1.51)	1.01 (0.52-1.95)	1.26 (0.69-2.29)	0.72 (0.37-1.42)	0.96 (0.56-1.65)	1.01 (0.55-1.85)	0.86 (0.49-1.52)	0.84 (0.39-1.8)	1.03 (0.5-2.13)	0.87 (0.44-1.7)	0.76 (0.37-1.55)	0.96 (0.34-2.69)	0.6 (0.26-1.4)	0.85 (0.45-1.6)				
S(2)	1.71 (0.95-3.08)	1.63 (1.29-2.07)	0.62 (0.4-0.95)	1.06 (0.87-1.3)	1.19 (0.76-1.87)	1.49 (1.05-2.13)	0.86 (0.54-1.37)	1.14 (0.89-1.46)	1.19 (0.83-1.74)	1.02 (0.76-1.38)	0.99 (0.56-1.79)	1.22 (0.71-2.11)	1.03 (0.65-1.64)	0.9 (0.53-1.53)	1.13 (0.45-2.82)	0.71 (0.36-1.42)	1.01 (0.67-1.52)	1.18 (0.69-2.03)			
S	1.65 (0.94-2.93)	1.58 (1.33-1.89)	0.6 (0.4-0.9)	1.03 (0.91-1.17)	1.16 (0.76-1.77)	1.45 (1.05-1.99)	0.83 (0.54-1.3)	1.1 (0.91-1.35)	1.16 (0.83-1.63)	0.99 (0.77-1.28)	0.96 (0.55-1.71)	1.18 (0.7-2)	0.99 (0.64-1.56)	0.87 (0.53-1.45)	1.09 (0.44-2.71)	0.69 (0.36-1.36)	0.98 (0.67-1.43)	1.14 (0.69-1.93)	0.97 (0.83-1.14)		
R	2.62 (1.46-4.77)	2.51 (1.95-3.22)	0.95 (0.61-1.47)	1.64 (1.32-2.03)	1.83 (1.17-2.91)	2.29 (1.59-3.3)	1.32 (0.82-2.13)	1.75 (1.34-2.28)	1.84 (1.26-2.7)	1.57 (1.15-2.14)	1.53 (0.85-2.78)	1.87 (1.08-3.27)	1.58 (0.98-2.55)	1.38 (0.82-2.37)	1.74 (0.69-4.37)	1.09 (0.55-2.2)	1.55 (1.02-2.36)	1.81 (1.12-2.95)	1.54 (1.21-1.95)	1.58 (1.33-1.89)	

b

	LTR	S+TTF	S+Bev	S+Nim	S+CpG	S+Cil(1)	S+Rin	S+Los	S(2)	S	R
S+TTF	1.03 (0.54-1.97)										
S+Bev	1.56 (0.81-2.98)	1.51 (0.91-2.49)									
S+Nim	1.44 (0.4-5.21)	1.4 (0.41-4.69)	0.93 (0.28-3.11)								
S+CpG	2.38 (0.77-7.25)	2.3 (0.81-6.47)	1.53 (0.54-4.29)	1.68 (0.38-7.37)							
S+Cil(1)	1.71 (0.94-3.08)	1.65 (1.08-2.52)	1.09 (0.72-1.67)	1.2 (0.38-3.74)	0.73 (0.27-1.92)						
S+Rin	1.67 (0.78-3.57)	1.62 (0.86-3.05)	1.08 (0.57-2.03)	1.18 (0.34-4.03)	0.71 (0.24-2.11)	0.98 (0.55-1.75)					
S+Los	1.53 (0.35-6.67)	1.48 (0.36-6.09)	0.98 (0.24-4.04)	1.08 (0.18-6.32)	0.65 (0.12-3.46)	0.9 (0.22-3.59)	0.92 (0.21-3.98)				
S(2)	1.98 (1.05-3.71)	1.92 (1.19-3.07)	1.27 (0.79-2.03)	1.39 (0.43-4.42)	0.84 (0.31-2.3)	1.16 (0.78-1.72)	1.19 (0.64-2.19)	1.31 (0.34-5.03)			
S	1.67 (0.96-2.88)	1.62 (1.14-2.3)	1.07 (0.75-1.53)	1.17 (0.38-3.57)	0.71 (0.27-1.84)	0.98 (0.77-1.24)	1 (0.59-1.69)	1.11 (0.29-4.08)	0.84 (0.62-1.15)		
R	3.2 (1.51-6.74)	3.1 (1.66-5.75)	2.06 (1.1-3.83)	2.25 (0.66-7.68)	1.36 (0.46-4.01)	1.88 (1.07-3.3)	1.92 (0.92-4)	2.12 (0.51-8.63)	1.62 (0.89-2.94)	1.92 (1.15-3.19)	

c

	S+TTF	S+Bev	S+Nim	S+CpG	S+Cil(1)	S+Cil(2)	S+Rin	S+Los	PRT	BRBI	S(2)	S	R
S+Bev	1.39 (0.99-1.95)												
S+Nim	1.24 (0.66-2.33)	0.89 (0.49-1.62)											
S+CpG	2.23 (1.19-4.18)	1.6 (0.88-2.92)	1.81 (0.82-4.01)										
S+Cil(1)	1.05 (0.67-1.64)	0.76 (0.51-1.13)	0.85 (0.44-1.65)	0.47 (0.24-0.91)									
S+Cil(2)	1.31 (0.85-2.02)	0.94 (0.64-1.39)	1.07 (0.56-2.03)	0.59 (0.31-1.12)	1.25 (0.77-2.02)								
S+Rin	1.6 (1.06-2.43)	1.15 (0.79-1.67)	1.3 (0.69-2.45)	0.72 (0.38-1.36)	1.52 (0.95-2.43)	1.22 (0.77-1.93)							
S+Los	1.39 (0.5-3.87)	1 (0.37-2.73)	1.13 (0.37-3.51)	0.63 (0.2-1.95)	1.33 (0.47-3.77)	1.06 (0.38-3.01)	0.87 (0.31-2.45)						
PRT	2.18 (1.08-4.4)	1.57 (0.8-3.08)	1.77 (0.76-4.17)	0.98 (0.42-2.3)	2.08 (1-4.33)	1.67 (0.81-3.44)	1.36 (0.67-2.8)	1.58 (0.5-4.93)					
BRBI	1.55 (0.98-2.46)	1.12 (0.73-1.7)	1.26 (0.65-2.46)	0.7 (0.36-1.36)	1.48 (0.89-2.46)	1.19 (0.72-1.95)	0.97 (0.6-1.57)	1.13 (0.41-3.05)	0.71 (0.34-1.48)				
S(2)	1.51 (1.08-2.11)	1.08 (0.82-1.43)	1.22 (0.68-2.2)	0.68 (0.37-1.22)	1.43 (0.96-2.13)	1.15 (0.78-1.69)	0.94 (0.65-1.36)	1.09 (0.41-2.83)	0.69 (0.36-1.34)	0.97 (0.64-1.47)			
S	1.52 (1.16-2)	1.09 (0.9-1.33)	1.24 (0.71-2.15)	0.69 (0.39-1.19)	1.45 (1.02-2.05)	1.16 (0.84-1.62)	0.95 (0.7-1.3)	1.1 (0.43-2.8)	0.7 (0.37-1.31)	0.98 (0.68-1.42)	1.01 (0.83-1.23)		
R	2.27 (1.38-3.71)	1.63 (1.03-2.57)	1.85 (0.92-3.67)	1.02 (0.51-2.03)	2.16 (1.26-3.69)	1.73 (1.02-2.93)	1.42 (0.85-2.37)	1.64 (0.58-4.55)	1.04 (0.49-2.21)	1.46 (0.84-2.54)	1.51 (0.95-2.37)	1.49 (0.99-2.25)	

d

	LTR	S+TTF	S+Eve	S+Bev	S+Nim	S+CIK	S+Cil(1)	S+Cil(2)	PRT	S(2)	S
S+TTF	0.84 (0.07,10.20)										
S+Eve	4.04 (0.33, 51.65)	4.76 (0.39, 60.76)									
S+Bev	1.39 (0.12, 17.07)	1.64 (0.15,19.91)	0.35 (0.03, 4.11)								
S+Nim	3.66 (0.28,50.06)	4.36 (0.34,59.79)	0.91 (0.07,12.82)	2.62 (0.21,33.50)							
S+CIK	1.14 (0.09, 13.61)	1.35 (0.11,16.04)	0.29 (0.02, 3.57)	0.82 (0.07, 9.55)	0.31 (0.02, 4.05)						
S+Cil(1)	0.92 (0.11, 8.26)	1.09 (0.14, 9.88)	0.23 (0.03, 2.13)	0.67 (0.09, 5.55)	0.26 (0.03, 2.44)	0.81 (0.10, 7.77)					
S+Cil(2)	0.89 (0.07, 10.74)	1.07 (0.09,12.85)	0.22 (0.02, 2.58)	0.65 (0.05, 7.33)	0.25 (0.02, 3.17)	0.80 (0.06, 9.73)	0.97 (0.10, 7.90)				
PRT	2.13 (0.15, 32.57)	2.50 (0.18,37.64)	0.52 (0.04, 8.17)	1.53 (0.11,21.81)	0.58 (0.04, 9.34)	1.84 (0.14,29.80)	2.26 (0.21,25.41)	2.36 (0.16,39.30)			
S(2)	1.54 (0.13, 19.01)	1.84 (0.17,22.15)	0.39 (0.03, 4.69)	1.13 (0.10,12.66)	0.43 (0.03, 5.46)	1.37 (0.12,18.04)	1.69 (0.19,13.64)	1.73 (0.15,21.79)	0.74 (0.05,10.53)		
S	0.72 (0.12, 4.17)	0.86 (0.15, 4.94)	0.18 (0.03, 1.08)	0.52 (0.09, 2.81)	0.20 (0.03, 1.25)	0.63 (0.11, 3.91)	0.78 (0.22, 2.58)	0.81 (0.13, 5.11)	0.34 (0.04, 2.51)	0.46 (0.08, 2.54)	

of bias (Online Resource Appendix 2). A relatively symmetric funnel plot demonstrated that no significant publication bias was detected (Online Resource Appendix 3). Results of assessing the quality of evidence using the GRADE system indicated that the quality of most evidence was low or very low (Online Resource Appendix 4).

Results of sensitivity analyses

Overall, no unacceptable change between pooled results and Bayesian ranking results was observed compared with the primary analysis (Online Resource Appendices 5 and 6). It is worth noting that some ranking change was caused by the different inclusion criteria of different sensitivity analyses. For instance, standard cilengitide combined with standard therapy replaced TTF combination treatment as the best in patients with unmethylated *MGMT* promoter in the second sensitivity analysis. In particular, the fourth sensitivity analysis demonstrated that treatments originally ranked first would rank first with higher possibility for Bayesian ranking results and the ORs became smaller while the CI became wider for the pooled results after excluding five trials in which randomization happened after chemoradiation (Bayesian ranking results of different sensitivity analyses are summarized in Appendix 7).

Discussion

The main findings of the present analysis are the following.

First, the primary network analysis demonstrated that TTF combination therapy was associated with significantly improved survival compared with other combination therapies. And LTR showed no different effect when compared with TTF combination treatment. In included studies, not all trials included both patients with and without *MGMT* promoter methylation. These trials merely provided HRs from patients with specific *MGMT* promoter, which were compared with HRs from trials that did not limit the type of *MGMT* promoter to enrich this comparison network. For trials with three kinds of HR results (including all patients, patients with *MGMT* promoter methylation, and patients without *MGMT* promoter methylation), results for all patients were applied to the primary analysis, and results for patients with different *MGMT* promoter statuses were applied to subgroup analysis. Hence, based on current evidence, we could not tell whether LTR was equally effective with TTF combination therapy for both patients with and without *MGMT* promoter methylation.

Second, subgroup analysis indicated that the optimal option for patients with different *MGMT* promoter statuses might change, which was likely to be related to two reasons. On the one hand, some therapies were only applied to treat GBM patients with a specific type of *MGMT* promoter in included studies, which caused some treatments to be excluded from the inconsistent subgroup. For example, the trial [4] only recruited GBM patients with methylated *MGMT* promoter, so LTR could not take part in the comparison for patients with unmethylated *MGMT* promoter in subgroup analysis. On the other hand, some treatments might have a preferable effect on patients with a specific *MGMT* promoter type. For instance, two studies involved standard cilengitide combined with standard therapy treating GBM patients. However, one trial [29] only recruited patients with methylated *MGMT* promoter, and one trial [38] only included patients with unmethylated *MGMT* promoter. Standard cilengitide combination therapy showed a preferable effect on OS in patients with unmethylated *MGMT* promoter compared with patients with methylated *MGMT* promoter. The preferable effect of standard cilengitide combination therapy for patients with unmethylated *MGMT* promoter might be neutralized on primary analysis. In the subgroup analysis, the preferable effect of standard cilengitide combination therapy showed up again due to the disappearance of the mixed population property. These two reasons might contribute to the change of the optimal treatment in patients with different *MGMT* promoter statuses. Furthermore, the results indicated that irrespective of the *MGMT* promoter status, TTF combination therapy improved OS significantly compared with other treatments.

Third, toxicity analysis suggested that combination treatments, including TTF combination therapy, might cause more toxicity than standard therapy alone within all comparable 11 treatments. Furthermore, TTF combination therapy was likely to generate less toxicity compared with the other seven combination treatments. Although some treatments were excluded in the safety comparison, the current results of the AEs ≥ 3 comparison could provide some reference value because

Fig. 3 Network diagrams and Bayesian ranking profiles. **a** Comparisons on overall survival (red line) and adverse events of grade 3 or higher (blue line) in patients with glioblastoma. **b** Comparisons on overall survival (red line) in glioblastoma patients with different statuses of MGMT promoter. Each circular node represents a one kind of treatment. The node size is proportional to the total number of patients receiving a treatment (in square brackets). Each line represents one kind of head-to-head comparison. The width of lines is proportional to the number of trials comparing the connected treatments. **c** Profiles indicate the probability of each comparable treatment being ranked from first to last on overall survival and adverse events of grade 3 or higher. mMGMT, methylated O-6-methylguanine-DNA methyltransferase; umMGMT, unmethylated O-6-methylguanine-DNA methyltransferase; LTR, lomustine-temozolomide (six courses)/radiotherapy (first course); S+Cil(1), Stupp + standard cilengitide; BRBI, bevacizumab/radiotherapy + bevacizumab/irinotecan; S+Cil(2), Stupp + intensive cilengitide; PRT, paclitaxel poliglumex/radiotherapy + TMZ; S+Los, Stupp + losartan; S+TTF, Stupp + TTFields; S+Rin, Stupp + rindopepimut; S+CpG, Stupp + CpG-ODN; S+Nim, Stupp + nimotuzumab; S+Bev, Stupp + bevacizumab; S+ICT, Stupp + ICT; S+Aud, Stupp + Audencel; HTT, HART/TMZ + TMZ; S+IFN, Stupp + interferonβ; S+CIK, Stupp + cytokine-induced killer; S+Eve, Stupp + everolimus; S(1), first kind of adjusted Stupp protocol; S(2), second kind of adjusted Stupp protocol; R, radiotherapy; S, Stupp protocol


a
S+TTF
[466][456]
S+Aud
[34]
S+Nim
[71][71]
S(2)
[422][369]
BRBI
[116]
S+Cil(2)
[88][81]
S+CIK
[91][85]
S+Bev
[770][461]
S+Rin
[195]
S+CpG
[39]
S+Los
[37]
S+IFN
[59]
PRT
[42][41]
S+ICT
[81]
S
[2792][1773]
S(1)
[57]
HTT
[45]
LTR
[66][66]
S+Eve
[88][85]
S+Cil(1)
[360][352]
R
[339]
1 trial
2 trials
Overall survival
Grade ≥3 adverse events
b
S+TTF
mMGMT: [137]
umMGMT: [209]
S(2)
mMGMT: [123]
umMGMT: [263]
S+Nim
mMGMT: [15]
umMGMT: [33]
S+Bev
mMGMT: [117]
umMGMT: [226]
BRBI
umMGMT: [116]
S+Rin
mMGMT: [69]
umMGMT: [107]
S+Cil(2)
umMGMT: [88]
S+Los
mMGMT: [12]
umMGMT: [21]
PRT
umMGMT: [42]
S
LTR
mMGMT: [66]
S+Cil(1)
mMGMT: [824]
umMGMT: [1088]
mMGMT: [272]
umMGMT: [88]
R
S+CpG
mMGMT: [46]
umMGMT: [54]
mMGMT: [10]
umMGMT: [25]
c
Probability(%)
LTR
S+TTF
S+Eve
S+Bev
S+Nim
S+CIK
S+Cil(1)
S+Cil(2)
PRT
S(2)
S
S+CpG
S+Rin
S+Los
BRBI
R
S+Aud
S+ICT
S+IFN
HTT
S(1)
Overall survival
methylated MGMT Overall survival
unmethylated MGMT Overall survival
adverse events of grade 3 or higher

almost all treatments that could significantly improve OS participated in the comparison of AEs. Moreover, the data sparseness might explain why some treatments had very large CIs in the toxicity analysis. These findings might only apply to patients with reasonable performance status because the patients who participated in these included trials usually have reasonable performance statuses.

We initially found 22 eligible trials; however, treatments extending the periods of temozolomide use were not uniformly limited to 12 cycles, and the Bhandari study [40] had inherent flaws, such as the fact that only provided Kaplan-Meier curves were provided and results were drawn from 40 small samples. Therefore, this study was excluded, and our analysis finally included 21 RCTs. In the included trials, the majority merely provided the OS outcomes of different methylation statuses of the *MGMT* promoter, and the standards [41, 42] of assessing disease progression were different; we therefore chose the OS, but not progression-free survival (PFS), as the primary efficacy indicator. Nevertheless, the possibility that salvage therapies enhancing survival bring confounding variables should be considered. Additionally, the extracted CI related to the HR from cytokine-induced killer (CIK) combination therapy was a 90% CI, instead of 95%. To avoid bigger errors caused by software fitting, we directly applied it to the pooled analysis, which led to CIK combination therapy showing significant differences, but CI nearly crossed one. However, Kong et al. reported that CIK combination therapy could only improve PFS but not OS. Compared with Li's study [6], this analysis was more comprehensive, and the results were tested more sufficiently. Moreover, included RCTs in this analysis were different from those included in two other recently published network meta-analyses [43, 44] aiming at determining the optimal treatment for the elderly with GBM, which indirectly supports the validity of strict restriction of the population in this analysis.

Limitations

This study has several limitations. First, some trials were excluded because of the failure of meeting the inclusion and exclusion criteria. Treatments from those trials were essentially different from all included treatments in this analysis, dissatisfying the principle of network meta-analysis (comparing two treatments via a third common one). Additionally, with respect to AEs ≥ 3, we recommend interpreting the current results cautiously because not all included treatments participated in the safety comparison. It remains unclear whether the excluded treatments affected the experimental results. However, we failed to obtain additional data for safety outcome analyses and unpublished data. Thus, publication bias cannot be ruled out.

Second, transitivity is a pivotal base of the network meta-analysis [45]. Previous studies [46–49] demonstrated that confounding factors such as age, Karnofsky performance status, the extent of resection, and the *MGMT* promoter methylation status affect the prognosis of patients with GBM. Although this analysis set strict inclusion and exclusion criteria to ensure the homogeneity of the study population, the aforementioned potential biases were unavoidable.

Third, attention should be paid to heterogeneity between study designs as such. For instance, some studies only recruited patients with a specific type of *MGMT* promoter, and some studies failed to report the situation of the *MGMT* promoter. It also remains unclear whether those treatments had better or worse effects for a specific type of *MGMT* promoter. Moreover, the homogeneity of the study population stratified by the status of *MGMT* was unclear. Therefore, there is a possible risk of inconsistency.

Fourth, almost all direct evidence was from one trial. Moreover, the low and very low-quality evidence, according to the GRADE, limits the ability to draw firm conclusions from our meta-analysis. We highlight that all interpretations of the results of this analysis should take their reliance on previous distributions and assumptions of transitivity and consistency into consideration, although we have conducted sensitivity analyses and investigated the heterogeneity.

Implications

The significant survival benefit and tolerated toxicity of adding TTF into standard therapy might support its possible use in combination with other valuable treatment options. Previous studies [13, 50, 51] demonstrated that TTF or lomustine plus temozolomide caused relative accepted toxicity and results from a recent bicentric retrospective analysis with 16 patients preliminarily indicated that TTF combining with lomustinetemozolomide for patients with methylated *MGMT* had potentially beneficial effects [52]. Future RCTs should pay attention to those possible effective strategies, such as the above triple therapy for patients with methylated *MGMT*.

Conclusion

In this network meta-analysis, with respect to OS, TTF combination therapy was related to significantly improved survival for both patients with and without *MGMT* promoter methylation compared with other treatments. Subgroup analyses indicated that lomustinetemozolomide plus radiotherapy and standard cilengitide combined with standard therapy appear to be equally effective as TTF combination therapy for patients with methylated or unmethylated *MGMT* promoter.

Concerning AEs, combination therapies might be associated with more toxicity compared with standard therapy alone. Between combination treatments, TTF combination therapy is likely to cause less toxicity, and everolimus combination therapy is likely to cause more toxicity. These findings are useful to improve the current standard of care and design novel combination therapies for adult patients with newly diagnosed GBM.

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Compliance with ethical standards

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

Ethical approval Not applicable

Informed consent Not applicable

Code availability Stata (version 13.0); OpenBUGS (version 3.2.3); R (version 3.6.3)

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