Neurology Asia 2017; 22(1) : 49 – 58

A network meta-analysis of treatment for newly diagnosed glioblastoma based on radiotherapy plus temozolomide

[*1,2,3]Mao-hua Zheng, [*4]Hong-tao Sun, [1]Ji-guang Xu, [1]Yong-hong Zhang, [1]Gang Yang, [1]Lei-ming Huo, [2,3]Jin-hui Tian, [2,3]Ke-hu Yang
[*]Mao-hua Zheng and Hong-tao Sun contributed equally to this work.

[1]Department of Neurosurgery, First Clinical Medical College of Lanzhou University, Lanzhou; [2]Evidence-based Medicine Center of Lanzhou University, Lanzhou; [3]Key Laboratory of Evidence-based Medicine and Knowledge Translation of Gansu Province, Lanzhou, China; [4]Department of Neurosurgery, Affiliated Hospital, Medical College of Chinese People's Armed Police, Tianjin, China

Abstract

Background & Objective: Radiotherapy and temozolomide are the standard therapy for newly diagnosed glioblastoma multiforme (GBM). However, it is unclear whether adding another agent to the commonly used radiotherapy-temozolomide (RT + TMZ) benefits newly diagnosed GBM patients. The present network meta-analysis aimed to assess the efficacy of combining other agents with RT + TMZ for GBM treatment.
Methods: A comprehensive literature search was conducted on PubMed, EMBASE.com, Web of Science, and the Cochrane Central Register of Controlled Trials from inception to September 23, 2014, to include all randomized controlled trials of RT + TMZ-based therapy in GBM patients. Pairwise and network meta-analyses were performed to compare the therapeutic regimens. *Results:* Seventeen studies involving 4,148 patients were identified. The results of pairwise meta-analysis indicated no significant differences among most comparison groups, except for bevacizumab + RT + TMZ versus RT + TMZ for progression-free survival (hazard ratio [HR] = 0.71, 95% confidence interval [CI]: 0.59–0.86; P = 0.000) and RT + TMZ versus RT alone for overall survival (HR = 0.71, 95% CI: 0.58–0.88; P = 0.001). The results of network meta-analysis also showed no significant differences in most comparisons; however, adverse events were more common among patients receiving additional therapeutic agents other than RT + TMZ. The ranking probability analysis indicated that bevacizumab + RT + TMZ and nimustine + cisplatin + RT + TMZ were associated with the best progression-free and overall survival, but they also caused the most adverse events in GBM patients. RT + bevacizumab + irinotecan had the highest probability of being the best regimen for minimizing adverse events.
Conclusions: The addition of other targeted agents, particularly bevacizumab and nimustine, to RT + TMZ could be slightly effective for the treatment of newly diagnosed GBM patients; however, adverse events remained common.

Keywords: newly diagnosed glioblastoma; radiotherapy; temozolomide; network meta-analysis; randomized controlled trials

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common and deadliest primary brain malignancy, with an annual prevalence of 2–3 new cases per 100,000 persons in Europe and North America.[1] The disease is more common in men than in women with an incidence rate ratio of 1.26:1.[2,3] The prognosis of GBM is particularly poor with a median survival of 15 months.[4] Despite the international efforts spent during the last decade, GBM treatment remains one of the most challenging and urgent tasks in clinical oncology.[5] The current therapeutic options for GBM include surgical resection, radiotherapy, and chemotherapy.[6] However, there are serious limitations to most treatments owing to the disease's anatomical location as

Address correspondence to: Ke-hu Yang, Evidence-based Medicine Center of Lanzhou University; Key Laboratory of Evidence-based Medicine and Knowledge Translation of Gansu Province. No. 199, Dong-gang West Road, Chengguan District, Lanzhou City, Gansu Province, China. Tel: +86-0931-8915076, Email: kehuyangebm2006@163.com

well as its complex biology and heterogeneity.[5,7] Furthermore, many chemotherapeutic agents are unable to penetrate the blood-brain barrier in order to exert their effects.[5] Additionally, GBM tumor cells have been found resistant to radiotherapy.[8]

Multiple clinical trials have been conducted to assess the efficacy and safety of different treatment plans for GBM, and their findings help define the current standard of care for patients with newly diagnosed disease.[6] Such a treatment consists of surgical resection, followed by adjuvant radiotherapy at 5000–6000 cGy and temozolomide (TMZ) for at least six months.[9] Previous systematic review suggests that radiotherapy/TMZ might provide better survival outcomes than radiotherapy alone in newly diagnosed GBM patients. However, such outcomes remain poor despite aggressive treatment with both radiotherapy and TMZ. Therefore, in order to further improve GBM treatment, novel therapeutic regimens, including the addition of other agents (e.g., bevacizumab, cilengitide, or irinotecan) to the standard radiotherapy and TMZ, and hypofractionated or three-dimensional conformal radiotherapy with concurrent and adjuvant TMZ, need to be explored. Several randomized controlled trials (RCTs) are currently available to compare between radiotherapy-TMZ and other therapeutic regimens in GBM. The results of these studies would certainly help determine whether radiotherapy-TMZ should remain as the standard of care for GBM.

In the present study, we aimed to conduct a network meta-analysis to compare the efficacy and safety of different radiotherapy-TMZ based therapeutic regimens for GBM and to rank those treatment plans.

METHODS

Search strategy

The reporting of this network meta-analysis adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[10] A comprehensive literature search was conducted on PubMed, EMBASE.com, Web of Science (via ISI Web of Knowledge), and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to September 23, 2014, using the following terms: glioma, glioblastoma, radiotherapy, brachytherapy, radiation therapy, radiosurgery, hypofraction, irradiation therapy, and random*. The references of included articles and reviews were tracked to identify other relevant studies. The complete detail of the search strategy for PubMed was as followed: (((((((“Glioma”[Mesh]) OR “Glioblastoma”[Mesh])) OR ((Glioma OR glioblastoma[Title/Abstract])))) AND ((((Radiotherapy OR brachytherapy OR “radiation therapy” OR radiosurgery OR “irradiation therapy”[Title/Abstract])))) OR ((“Radiotherapy”[Mesh] OR “radiotherapy” [Subheading] OR “Radiotherapy, Adjuvant”[Mesh])))))) AND (((Random* OR randomized controlled trial* OR randomized trial* OR Randomized Controlled Trial[ptyp] OR “Randomized Controlled Trials as Topic”[Mesh]) NOT (“Clinical Trial, Phase I” [Publication Type] OR “Clinical Trial, Phase II” [Publication Type] OR “Clinical Trials, Phase I as Topic”[Mesh] OR “Clinical Trials, Phase II as Topic”[Mesh]))). The latest version of duplicated publications was included in the study.

Inclusion criteria

All RCTs met the following eligibility criteria were included: (1). The trials enrolled newly diagnosed GBM patients who had undergone surgery (complete or partial resection, or biopsy only) but had not received prior radiotherapy or chemotherapy; (2). The treatment arms consisted of radiotherapy, followed by adjuvant or subsequent TMZ; and (3). The primary outcomes included progression-free survival (PFS) and overall survival (OS), whereas the secondary outcomes mainly included adverse events (AEs). We only included RCTs in our analysis, with non-randomized, phase I, and phase II clinical trials being excluded.

Data extraction and assessment of risk of bias

Two independent reviewers examined the title, abstract, and full-text of all studies according to the inclusion and exclusion criteria to extract data. A third reviewer’s opinion was used to resolve discrepancy. Data of interest were extracted using a standard form that included information on authors, journal, year of publication, study arms, sample, median age, median OS, median PFS, dosage of radiotherapy, and outcomes. The methodological quality was evaluated according to the Cochrane Handbook version 5.1.0[11], including the method of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases.

Data analysis

Direct comparison was performed using STATA 12.0 software, and pooled hazard ratio (HR) was determined from the HR values reported for PFS and OS. Relative risk (RR) was determined for AEs as they were dichotomous variables. Statistical heterogeneity between trials was assessed by χ^2 statistic, whereas I^2 statistic was used to assess the extent of inconsistency. When there was no statistical heterogeneity, indicated by a P value of >0.05 and I^2 of <50%, the Mantel-Haenszel fixed effects model was used for meta-analysis, otherwise the Mantel-Haenszel random effects model was used. Moreover, a Bayesian network meta-analysis was performed using WinBUGS 1.4 software for the indirect comparison of all available therapeutic regimens. A ranking probability curve was generated for each regimen to estimate its probability of achieving the best rank among all. The pooled estimates and probability of the potential best regimen were obtained using the Markov Chains Monte Carlo method. The random effect model for multi-arm trials developed by Ade and colleagues (the Multi-Parameter Evidence Synthesis Research Group at the University of Bristol, UK; downloaded 20 March 2015 from http://www.bristol.ac.uk/social-community-medicine/projects/mpes/mtc/) was used. We generated 50,000 simulations for the initial values, and subsequently discarded the first 10,000 simulations as the burn-in period. The inconsistency between direct and indirect comparisons was not evaluated because no close loop existed. All pairwise meta-analysis results were reported with 95% confidence intervals (CI), whereas those of the network meta-analyses were with 95% credibility interval (CrI), as well as the probability of ranking by regimens. Statistical significance was defined as P value ≤0.05.

RESULTS

Characteristics of the included studies

Our literature search identified 2,043 records. Of these, 2,026 were excluded due to the following reasons: duplicated publications (n = 662), not RCTs (n = 1014), not GBM (n = 210), animal studies (n = 20), not radiotherapy + TMZ (n = 139), reviews (n = 70), or abstracts/letters/comments (n = 37). Thus, a total of 17 RCTs[12-28] involving 4,148 patients were included (Figure 1). The characteristics of these included studies

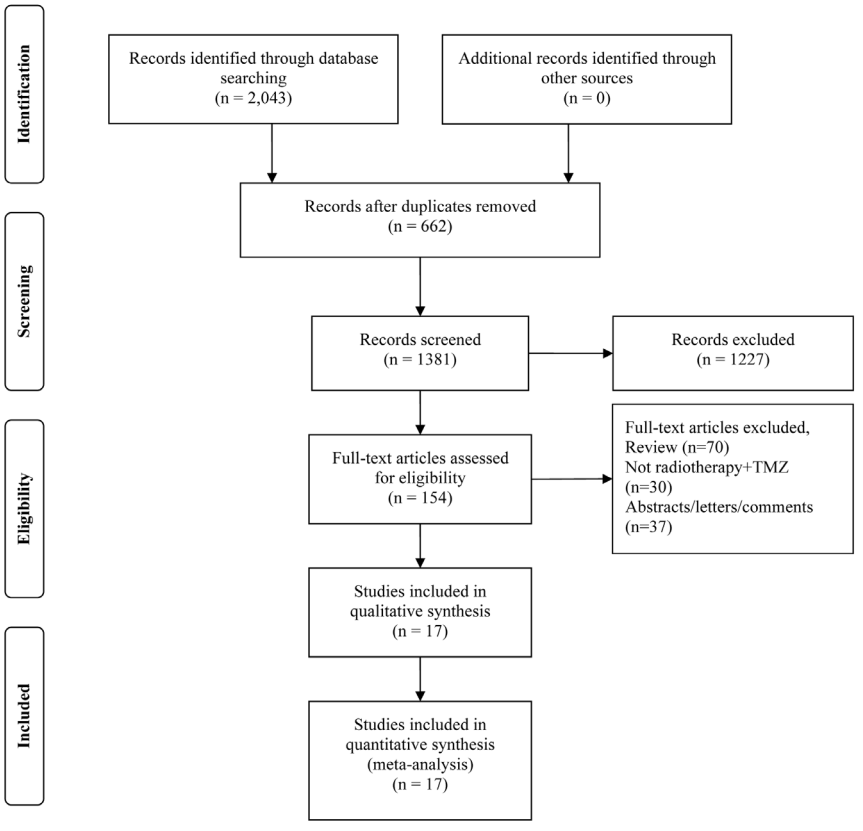

Figure 1. The search results and selection details

Table 1: Characteristics of included studies

Study	Journal	Multicenter?	Arm	Sample	Median age	Dosage of RT	Median PFS (months)	Median OS (months)	Outcomes
Chinot OL 2014	The New England Journal of Medicine[12]	Yes	Bev+RT+TMZ	458	57 (20-84)	2Gy/30f/60Gy	10.6	16.8	abcd
			RT+TMZ	463	56 (18-79)		6.2	16.7	
Hofland KF 2014	Acta Oncologica[13]	Yes	Bev+RT+TMZ	32	62(30-73)	2Gy/30f/60Gy	7.7(5.1-10.2)	11.8(8.2-15.3)	abcd
			RT+Bev+Iri	31	59(36-77)		7.3(5.0-9.3)	15.1(9.6-20.6)	
Kim IH 2011	Journal of Neuro-Oncology[14]	Yes	ACNU+CDDP+RT+TMZ	40	51.4±12.4	1.8-2.0Gy/30f/60.0-61.2Gy	6.6(3.5-9.5)	28.4(21.1-NA)	abc
			RT+TMZ	42	51.1±11.8		5.1(3.8-8.8)	18.9(17.1-27.4)	
Zhai XM 2012	Journal of Southern Medical University[15]	No	RT+TMZ	48	NR	2Gy/30f/60Gy	NR	NR	cd
			CCNU+VM+RT	48	NR				
Shen ZT 2014	Cancer Research and Clinic[16]	NR	RT+TMZ	46	52(9-82)	1.8-2.0Gy/33f/60.0-66Gy	NR	22	bcd
			RT	46	48(13-75)			12	
Kocher M 2008	Strahlenther Onkol[17]	Yes	RT+TMZ	29	59(34-67)	2Gy/30f/60Gy	6.3(5.1-7.5)	14.6(12.0-17.2)	abc
			RT	33	58(37-69)		7.6(6.8-8.4)	17.1(13.5-20.8)	
Stupp R 2005	The New England Journal of Medicine[18]	Yes	RT+TMZ	287	56(19-70)	2Gy/30f/60Gy	6.9(5.8-8.2)	14.6(13.2-16.8)	abc
			RT	286	57(23-71)		5.0(4.2-5.5)	12.1(11.2-13.0)	
Stupp R 2014	Lancet Oncology[19]	Yes	Cil+RT+TMZ	272	58(50-65)	2Gy/30f/60Gy	13.5(10.8-15.9)	26.32(23.8-28.8)	abc
			RT+TMZ	273	58(50-64)		10.7(8.1-13.3)	26.32(23.9-34.7)	
Yaneva MP 2009	Folia Medica[20]	NR	RT+TMZ	44	NR	2Gy/30f/60Gy	NR	14.83(12.15-17.52)	bc
			RT	135	NR			15.43(12.73-18.13)	
Dai PY 2011	Chinese Journal of Cancer Prevention and Treatment[21]	No	RT+TMZ	15	36.9±17.5	2Gy/30f/60Gy	NR	NR	bcd
			RT	14	37.2±18.3				
Athanassiou H 2005	Journal of Clinical Oncology[22]	NR	RT+TMZ	57	NR	2Gy/30f/60Gy	10.8(8.08-14.69)	13.41(9.53-17.13)	abc
			RT	53	NR		5.2(3.94-7.36)	7.7(5.32-9.20)	
Cohen MH 2005	Clinical Cancer Research[23]	Yes	RT+TMZ	287	55(18-70)	2Gy/30f/60Gy	6.9	14.6	abc
			RT	286	56(23-70)		5	12.1	
Wang Q 2008	Chinese Journal of Cancer Prevention and Treatment[24]	No	RT+TMZ	18	NR	2Gy/30f/60Gy	21(5-36)	NR	abc
			RT	23	NR		17(3-25)		
Zhang YY 2012	Journal of Jilin University[25]	No	RT+TMZ	22	51(5-68)	2Gy/30f/60Gy	10	NR	abc
			RT	24			7.6		
Zheng RF 2013	Chinese Journal of Cancer Prevention and Treatment[26]	Yes	RT+TMZ	28	42(26-72)	2Gy/30f/60Gy	NR	32.6	abc
			RT	29				24.5	
Gilbert MR 2014	The New England Journal of Medicine[27]	Yes	Bev+RT+TMZ	312	NR	2Gy/30f/60Gy	10.7(10.0-12.2)	15.7(14.2-16.8)	abc
			RT+TMZ	309	NR		7.3(5.9-7.9)	16.1(14.8-18.7)	
Szczepanek D 2013	Neurologia I Neurochirurgia Polska[28]	Yes	RT+TMZ	28	55(18-65)	2Gy/30f/60Gy	7.5	16	abc
			RT	30	56(20-68)		5	12.5	

Note: NR, not report; a.PFS; b.OS; c.adverse event;d.ORR; RT, radiotherapy; TMZ, temozolomide; Bev, bevacizumab; Iri, irinotecan; ACNU, nimustine; CDDP, cisplatin ; VM, teniposide; CCNU, semustine; Cil, Cilengitide

are summarized in Table 1. Seven therapeutic regimens were analyzed, including radiotherapy alone (RT), radiotherapy + TMZ (RT + TMZ), bevacizumab + radiotherapy + TMZ (Bev + RT + TMZ), cilengitide + radiotherapy + TMZ (RT + TMZ + Cil), bevacizumab + radiotherapy + irinotecan (RT + Bev + Iri), teniposide + semustine + radiotherapy (CCNU + VM + RT), and nimustine + cisplatin + radiotherapy + TMZ (ACNU + CDDP + RT + TMZ). The total radiotherapy dose in all the included studies except for the one by Shen *et al.* was 60 Gy given in 30 fractions.[16] The following outcomes were analyzed PFS, OS, granulocytopenia, thrombocytopenia, and nausea as they were reported by most studies. The results of methodological quality assessment are presented in Figure 2. Of the included RCTs, 64.71% reported their methods of sequence generation, and 47.06% described the details of allocation concealment. Only 4 RCTs were designed as double-blinded studies.

Results of pairwise meta-analysis

Two studies[12,27] compared the PFS and OS of GBM patients receiving Bev + RT + TMZ and those treated with RT + TMZ. The Bev + RT + TMZ regimen significantly prolonged PFS (HR = 0.71, 95% CI: 0.59–0.86; P < 0.001) as compared to RT + TMZ in these patients (Figure 3). However, no statistically significant differences were observed for OS (HR = 0.99, 95% CI: 0.78–1.27; P = 0.961) (Figure 4). Moreover, Bev + RT + TMZ did not reduce the incidences of granulocytopenia (RR = 1.98, 95% CI: 0.98–4.01; P = 0.058), thrombocytopenia (RR = 1.33, 95% CI: 0.80–2.23; P = 0.272), and nausea (RR = 1.98, 95% CI: 0.18–21.72; P = 0.576).

Furthermore, 2 other studies[17,18] compared the PFS of GBM patients receiving RT + TMZ and those treated with RT alone, whereas 7 studies[16-18,20,22,23,26] analyzed OS. Their results indicated that compared with RT alone, RT + TMZ significant improved OS (HR = 0.71, 95% CI: 0.58–0.88; P = 0.001) (Figure 4). No statistically significant differences were observed for PFS (HR = 0.74, 95% CI: 0.40–1.35; P = 0.326) (Figure 3). However, RT + TMZ was inferior to RT alone in reducing AEs, such as granulocytopenia (RR = 1.29, 95% CI: 0.70–2.38; P = 0.408), thrombocytopenia (RR = 3.65, 95% CI: 1.03–12.96; P = 0.045), and nausea (RR = 2.11, 95% CI: 1.12–3.97; P = 0.576).

Only one study[13] compared the efficacy of Bev + RT + TMZ and RT + Bev + Iri. No statistically significant differences were observed for overall response rate (RR = 1.56, 95% CI: 0.96–2.54; P = 0.07), granulocytopenia (RR = 2.91, 95% CI: 0.32–26.46; P = 0.344), thrombocytopenia (RR = 14.55, 95% CI: 0.87–244.30; P = 0.063), or nausea (RR = 0.89, 95% CI: 0.49–1.65; P = 0.719).

In addition, no statistically significant differences in any outcomes were observed for other comparison groups. Such results are presented in Figure 3 and Figure 4.

Results of network meta-analysis

The results of our network meta-analysis indicated that RT + TMZ resulted in longer OS than RT alone. ACNU + CDDP + RT + TMZ led to a lower incidence of granulocytopenia than RT + TMZ and RT alone, whereas RT + Bev + Iri was associated with a lower frequency of thrombocytopenia than Bev + RT + TMZ. There were no statistically significant differences in other outcomes for all other comparison groups. The results of network meta-analysis are summarized in Tables 2–4.

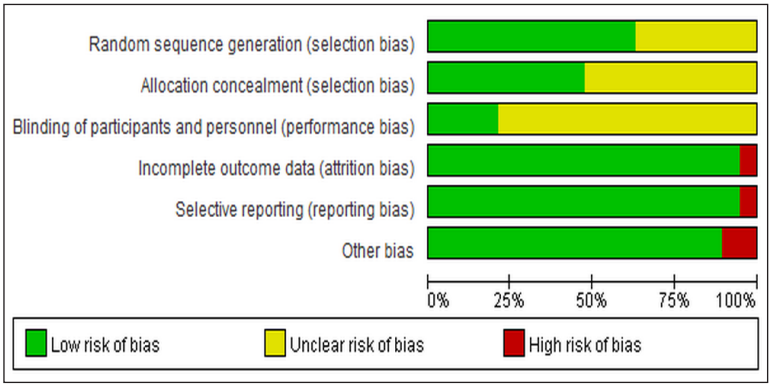

Figure 2. The results of risk of bias assessment

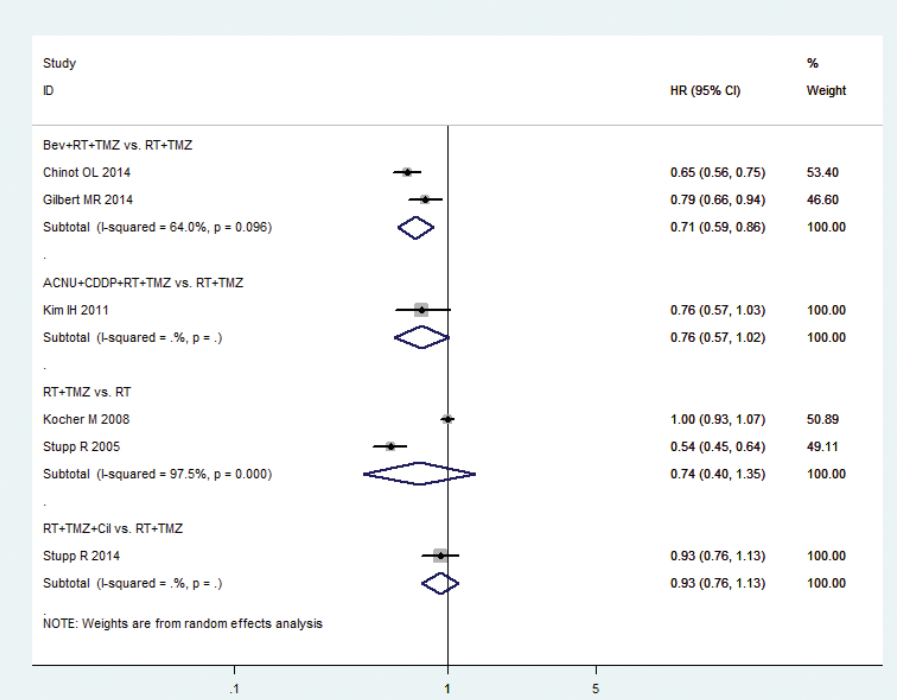

Figure 3. The results of pairwise meta-analysis for progression-free survival (PFS)

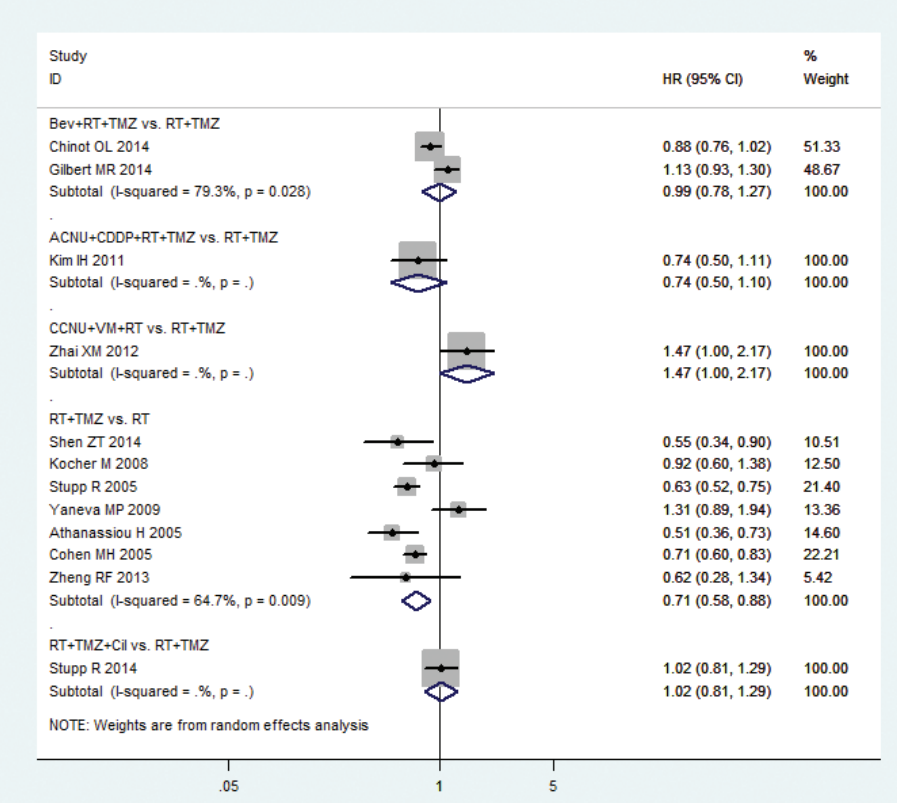

Figure 4. The results of pairwise meta-analysis for overall survival (OS)

Table 2: The results of network meta-analysis regarding PFS and OS [OR (95%CrI)

PFS	RT	RT+TMZ	Bev+RT+TMZ	ACNU+CDDP+RT+TMZ	CCNU+VM+RT	RT+TMZ+Cil
RT	-	1.41(1.04-1.85)	1.48(0.79-2.48)	2.05(0.82-4.25)	1.03(0.41-2.13)	1.46(0.63-2.83)
RT+TMZ	1.65(0.53-4.71)	-	1.05(0.63-1.66)	1.45(0.63-2.90)	0.73(0.32-1.46)	1.03(0.48-1.93)
Bev+RT+TMZ	2.82(0.59-11.73)	1.68(0.52-4.82)	-	1.48(0.52-3.30)	0.74(0.27-1.64)	1.05(0.40-2.22)
ACNU+CDDP+RT+TMZ	26.38(0.28-30.86)	8.57(0.24-18.18)	8.91(0.14-16.34)	-	0.59(0.17-1.48)	0.83(0.26-2.02)
CCNU+VM+RT	-	-	-	-	-	1.65(0.50-4.04)
RT+TMZ+Cil	3.85(0.21-15.62)	2.18(0.19-7.04)	1.37(0.09-5.96)	3.03(0.04-10.43)	-	**OS**

PFS, progression-free survival; OS, overall survival; RT, radiotherapy; TMZ, temozolomide; Bev, bevacizumab; Iri, irinotecan; ACNU, nimustine; CDDP, cisplatin ; VM, teniposide; CCNU, semustine; Cil, Cilengitide

Table 3: The results of network meta-analysis regarding granulocytopenia and thrombocytopenia [OR (95%CrI)

Granulocytopenia	RT	RT+TMZ	Bev+RT+TMZ	RT+Bev+Iri	ACNU+CDDP+RT+TMZ	RT+TMZ+Cil
RT	-	0.60(0.06-2.75)	0.53(0.02-2.88)	591.90(0.33-2043.00)	0.29(0.00-1.80)	1.39(0.04-8.33)
RT+TMZ	0.98(0.23-2.90)	-	1.05(0.06-4.63)	1951.00(0.83-6300.00)	0.55(0.01-3.12)	2.45(0.15-12.02)
Bev+RT+TMZ	0.67(0.06-3.09)	0.72(0.09-2.76)	-	4196.00(1.88-10980.00)	2.09(0.01-11.80)	10.31(0.13-52.81)
RT+Bev+Iri	7.08(0.09-46.13)	8.44(0.12-50.64)	13.84(0.32-79.80)	-	0.12(0.00-0.55)	0.58(0.00-2.61)
ACNU+CDDP+RT+TMZ	0.11(0.00-0.63)	0.12(0.0-0.66)	0.40(0.00-2.03)	0.18(0.00-1.06)	-	44.93(0.20-222.70)
RT+TMZ+Cil	-	-	-	-	-	**Thrombocytopenia**

RT, radiotherapy; TMZ, temozolomide; Bev, bevacizumab; Iri, irinotecan; ACNU, nimustine; CDDP, cisplatin ; VM, teniposide; CCNU, semustine; Cil, Cilengitide

Table 4 The results of network meta-analysis regarding nausea [OR (95%CrI)

Nausea	RT	RT+TMZ	Bev+RT+TMZ	RT+Bev+Iri	CCNU+VM+RT
RT	-	-	-	-	-
RT+TMZ	0.42(0.09-1.31)	-	-	-	-
Bev+RT+TMZ	0.99(0.01-6.29)	2.88(0.04-17.71)	-	-	
RT+Bev+Iri	2.03(0.01-13.71)	6.18(0.02-41.11)	3.59(0.06-22.17)	-	-
CCNU+VM+RT	0.55(0.01-3.52)	1.44(0.03-8.81)	5.71(0.01-36.57)	9.41(0.00-51.96)	-
RT+TMZ+Cil	1.35(0.02-8.31)	3.60(0.08-20.54)	13.19(0.02-87.13)	21.99(0.01-131.30)	20.94(0.05-135.20)

RT, radiotherapy; TMZ, temozolomide; Bev, bevacizumab; Iri, irinotecan; ACNU, nimustine; CDDP, cisplatin ; VM, teniposide; CCNU, semustine; Cil, Cilengitide

Rank probability

The rank probability plot (Table 5) indicated that Bev + RT + TMZ and ACNU + CDDP + RT + TMZ were associated with the longest PFS and OS in GBM patients, but they also resulted in the highest incidence of AEs. RT + Bev + Iri had the highest probability of being the best treatment plan for reducing AEs.

DISCUSSION

Summary of findings

The first systematic review comparing RT + TMZ and RT alone for the treatment of newly diagnosed GBM was published in 2014. However, a meta-analysis was not performed owing to a lack of homogeneity in their study. Their results demonstrated that GBM patients treated with RT + TMZ had consistently better survival outcomes than those receiving RT alone.[6] Our network meta-analysis compared the safety and efficacy of different RT + TMZ-based therapeutic regimens for newly diagnosed GBM. The results of our pairwise and network meta-analyses consistently indicated RT + TMZ was associated with longer OS than RT alone. However, although the pairwise meta-analysis results suggested that Bev + RT + TMZ resulted in statistically longer PFS than RT + TMZ, the network meta-analysis did not detect any statistically significant differences among different treatment plans. Moreover, although the pairwise meta-analysis indicated no statistically significant differences in AE incidence among therapeutic regimens, the network meta-analysis suggested that RT + Bev + Iri was associated with a lower incidence of thrombocytopenia than Bev + RT + TMZ. The ranking probability plot also suggested that the addition of bevacizumab or nimustine + cisplatin to RT + TMZ could potential prolong the PFS and OS of GBM patients. Of note, patients treated with radiotherapy followed by bevacizumab and irinotecan might experience less AEs. ACNU + CDDP + RT + TMZ led to a lower incidence of granulocytopenia than RT alone or RT + TMZ, however, ACNU + CDDP + RT + TMZ had the lowest probability of being the best treatment plan for reducing AEs. The reason was likely that only one study involving 82 patients was included for network meta-analysis.

Although several studies in newly diagnosed GBM patients recommend the standard

Table 5: Rank probability

Comparisons	PFS	OS	Nausea	Granulocytopenia	Thrombocytopenia
RT	0.01	0.00	**0.45**	0.29	0.06
RT+TMZ	0.03	0.04	0.01	0.12	0.01
Bev+RT+TMZ	**0.38**	0.13	0.10	0.02	0.00
ACNU+CDDP+RT+TMZ	**0.37**	**0.64**	-	0.00	0.01
CCNU+VM+RT	-	0.03	0.07	-	-
RT+TMZ+Cil	0.21	0.16	0.19	-	0.04
RT+Bev+Iri	-	-	**0.19**	**0.57**	**0.89**

RT, radiotherapy; TMZ, temozolomide; Bev, bevacizumab; Iri, irinotecan; ACNU, nimustine; CDDP, cisplatin ; VM, teniposide; CCNU, semustine; Cil, Cilengitide

multimodality treatment in combination with bevacizumab[29], there is no meta-analysis to assess the efficacy of bevacizumab for the treatment of newly diagnosed GBM. A recent phase II trial showed that the combination of bevacizumab with radiotherapy and TMZ was safe and feasible in patients with newly diagnosed GBM.[30] Zhang *et al.*[31] conducted a meta-analysis to compare the bevacizumab and irinotecan combination to bevacizumab alone for the treatment of recurrent GBM, and showed no obvious improvement in overall survival. We only identified one RCT involving 63 patients comparing the efficacy and safety of Bev + RT + TMZ versus RT + Bev + Iri for treating newly diagnosed GBM. Our findings on PFS and OS were similar to those of Zhang *et al.* Furthermore, we found that RT + Bev + Iri significantly reduced the incidence of AEs. Wang *et al.*[32] compared the clinical efficacy of TMZ versus ACNU-based chemotherapy in newly diagnosed GBM and showed that the treatment tolerance and survival benefit by TMZ therapy were superior to that of ACNU-based regimens. However, we found that the addition of ACNU-based chemotherapy to RT + TMZ was associated with the highest probability of improved PFS and OS, although no significant differences were detected by pairwise or network meta-analysis.

Strengths and limitations

To our knowledge, this is the first meta-analysis and network meta-analysis comparing different RT + TMZ-based treatment plans for newly diagnosed GBM. The methodological quality of included studies was high, although only 4 of the included RCTs were designed as double-blinded. However, as the outcomes we focused on were objective, the impact of non-blinding design was minimized in our study. Nonetheless, the present study also had some limitations. First, the number of studies that assessed the efficacy of adding other agents to RT + TMZ for the treatment of newly diagnosed GBM was limited. Therefore, although we found that the addition of other agents to RT + TMZ offered better efficacy for the treatment of newly diagnosed GBM, more studies are needed to confirm our findings. Moreover, we did not compare between hypo-fractionated or three-dimensional conformal radiotherapy and conventional radiotherapy owing to a lack of original studies. Finally, although our ranking probability showed that ACNU + CDDP + RT + TMZ was associated with the longest PFS and OS, and that RT + Bev + Iri had the highest probability of being the best treatment plan for reducing AEs, such conclusions were based on 2 studies with relatively small sample size. Therefore, more studies assessing the efficacy of ACNU + CDDP + RT + TMZ and RT + Bev + Iri in newly diagnosed GBM are certainly needed.

In conclusion, the addition of other targeted agents, particularly bevacizumab and nimustine, to the frequently used RT + TMZ could be slightly more effective for the treatment of newly diagnosed GBM patients; however, adverse events remained common. More studies on adding other targeted agents to RT + TMZ are needed to confirm our findings.

ACKNOWLEDGEMENTS

We gratefully acknowledge Professor Ke-hu Yang for his help in guiding and revising the manuscript. We also thank all the study participants.

DISCLOSURE

Conflict of Interest: None

REFERENCES

1. Verdecchia A, De Angelis G, Capocaccia R. Estimation and projections of cancer prevalence from cancer registry data. *Stat Med* 2002; 21:3511-26.
2. Mahvash M, Hugo HH, Maslehaty H, Mehdorn HM, Stark AM. Glioblastoma multiforme in children: report of 13 cases and review of the literature. *Pediatr Neurol* 2011; 45:178-80.
3. Urbańska K, Sokołowska J, Szmidt M, Sysa P. Glioblastoma multiforme - an overview. *Contemp Oncol (Pozn)* 2014; 18:307-12.
4. Wen PY, Kesari S. Malignant gliomas in adults. *N Engl J Med* 2008; 359: 492-507.
5. Mrugala MM. Advances and challenges in the treatment of glioblastoma: a clinician's perspective. *Discov Med* 2013; 15:221-230.
6. Yang LJ, Zhou CF, Lin ZX. Temozolomide and radiotherapy for newly diagnosed glioblastoma multiforme: a systematic review. *Cancer Invest* 2014; 32:31-6.
7. Kesari S. Understanding glioblastoma tumor biology: the potential to improve current diagnosis and treatments. *Semin Oncol* 2011; 38(Suppl 4):S2-S10.
8. Chang JE, Khuntia D, Robins HI, Mehta MP. Radiotherapy and radiosensitizers in the treatment of glioblastoma multiforme. *Clin Adv Hematol Oncol* 2007; 5:894-902.
9. Kanu OO, Mehta A, Di C, *et al*. Glioblastoma multiforme: a review of therapeutic targets. *Expert Opin Ther Targets* 2009;13:701-18.
10. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare

interventions: explanation and elaboration. *BMJ* 2009; 339:b2700.
11. Higgins JPT, Green S. Cochrance handbook for systematic reviews of interventions Version 5.1.0 [EB/OL]. The Cochrane Collaboration [2013.5.16]. http://www.cochrane-handbook.org.
12. Chinot OL, Wick W, Mason W, *et al*. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 2014; 370:709-22.
13. Hofland KF, Hansen S, Sorensen M, *et al*. Neoadjuvant bevacizumab and irinotecan versus bevacizumab and temozolomide followed by concomitant chemoradiotherapy in newly diagnosed glioblastoma multiforme: A randomized phase II study. *Acta Oncol* 2014; 53:939-44.
14. Kim IH, Park CK, Heo DS, *et al*. Radiotherapy followed by adjuvant temozolomide with or without neoadjuvant ACNU-CDDP chemotherapy in newly diagnosed glioblastomas:a prospective randomized controlled multicenter phase III trial. *J Neurooncol* 2011; 103:595-602.
15. Zhai X, Wang J, Zhang J, Gu K. Comparison of two regimens of postoperative concurrent chemoradiotherapy in adult patients with grade III-IV cerebral gliomas. *J South Med Univ* 2012; 32:255-7.
16. Shen ZT, Wu XB, Li B. Clinical effect of temozolomid combined with concurrent radiotherapy on high grade intracranial glioma. *Cancer Research and Clinic* 2014; 26:102-5.
17. Kocher M, Frommolt P, Borberg SK, *et al*. Randomized study of postoperative radiotherapy and simultaneous temozolomide without adjuvant chemotherapy for glioblastoma. *Strahlenther Onkol* 2008; 184:572-9.
18. Stupp R, Mason WP, van den Bent MJ, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; 352:987-96.
19. Stupp R, Hegi ME, Gorlia T, ,*et al*. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; 15:1100-8.
20. Yaneva MP, Semerdjieva ML, Radev LR, Vlaikova MI. Postoperative chemo-radiotherapy with temodal in patients with glioblastoma multiforme--survival rates and prognostic factors. *Folia Med (Plovdiv)* 2010; 52:26-33.
21. Dai PY, Wang SW, Zhang CR, Chen FQ. Three-dimensional conformal radiotherapy combined with temozolomide for the treatment of brain glioma. *Chinese Journal of Cancer Prevention and Treatment* 2011; 18:128-30.
22. Athanassiou H, Synodinou M, Maragoudakis E, *et al*. Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. *J Clin Oncol* 2005; 23:2372-7.
23. Cohen MH, Johnson JR, Pazdur R. Food and Drug Administration Drug approval summary: temozolomide plus radiation therapy for the treatment of newly diagnosed glioblastoma multiforme. *Clin Cancer Res* 2005; 11:6767-71.
24. Wang Q, Wang NY, Sheng HM. Clinical observation in temozolomide combined with radiotherapy in treatment of postoperative malignant glioma. *Chinese Journal of Cancer Prevention and Treatment* 2008; 15:843-5.
25. Zhang YY, Qu YQ, Jiang X. Evaluation of short-term efficacy and safety of intensity modulated radiation therapy plus concomitant and adjuvant temozolomide in patients with malignant gliomas. *Journal of Jilin University* 2012; 38:571-4.
26. Zheng RF, Fan RT, Wen HY. Postoperative intensity-modulated radiation therapy combined with concurrent TMZ chemotherapy for treatment of anaplastic astrocytoma. *Chinese Journal of Cancer Prevention and Treatment* 2013; 20:607-10.
27. Gilbert MR, Dignam JJ, Armstrong TS, *et al*. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 2014; 370:699-708.
28. Szczepanek D, Marchel A, Moskała M, Krupa M, Kunert P, Trojanowski T. Efficacy of concomitant and adjuvant temozolomide in glioblastoma treatment. A multicentre randomized study. *Neurol Neurochir Pol* 2013; 47:101-8.
29. Poulsen HS, Urup T, Michaelsen SR, Staberg M, Villingshj M, Lassen U. The impact of bevacizumab treatment on survival and quality of life in newly diagnosedglioblastoma patients. *Cancer Manag Res* 2014; 6:73-87l.
30. van Linde ME, Verhoeff JJ, Richel DJ, *et al*. Bevacizumab in combination with radiotherapy and temozolomide for patients with newly diagnosed glioblastoma multiforme. *Oncologist* 2015; 20:107-8.
31. Zhang G, Huang S, Wang Z. A meta-analysis of bevacizumab alone and in combination with irinotecan in the treatment of patients with recurrent glioblastoma multiforme. *J Clin Neurosci* 2012; 19:1636-40.
32. Wang Y, Chen X, Zhang Z, *et al*. Comparison of the clinical efficacy of temozolomide (TMZ) versus nimustine (ACNU)-based chemotherapy in newly diagnosed glioblastoma. *Neurosurg Rev* 2014; 37:73-8.