Int J Clin Exp Med 2019;12(2):1525-1534
www.ijcem.com /ISSN:1940-5901/IJCEM0079825

Original Article

Interferon combined with temozolomide for treatment of high-grade gliomas: a systematic review and meta-analysis

Dong Wang[1,6*], Zheng-Xing Gou[2,3*], Mei-Qing He[3], De-Qing Fan[4], Feng-Mei Wen[5], Hai-Bin Chen[6]

Departments of [1]Neurosurgery, [2]Nuclear Medicine, [3]Human Resources, [4]Hepatobiliary Surgery, [5]Science and Education, Fuling Central Hospital of Chongqing City, Chongqing 408000, China; [6]Department of Histology and Embryology, Shantou University Medical College, Shantou 515041, Guangdong, China. [*]Equal contributors.

Received May 17, 2018; Accepted December 12, 2018; Epub February 15, 2019; Published February 28, 2019

Abstract: Background: Combination therapy with interferon (IFN) and temozolomide (TMZ) for high-grade gliomas (HGG) has been assessed in several clinical trials with small sample sizes. The present systematic review and meta-analysis was performed to evaluate the overall efficacy of combination therapy with IFN and TMZ for HGG. Methods: Medline and EMBASE databases, along with the Cochrane Library (up to September 12, 2017), were searched to identify relevant studies. The primary outcome was tumor response. Secondary outcomes included progression-free survival (PFS), overall survival (OS), median PFS, and median OS. Results: Five studies, comprising 155 cases, were subjected to meta-analysis. As determined by a fixed-effects model, the overall clinical benefit rate was 68.8% (95% CI 59.3-77.0%; heterogeneity analysis: Q = 2.718, I^2 = 0.000, P = 0.437), overall PFS-6 rate was 35.4% (95% CI 25.8-46.3%; Q = 2.995, I^2 = 0.000, P = 0.392), and overall median PFS was 4.306 months (95% CI 3.231-5.380 months; Q = 2.554, I^2 = 0.000, P = 0.466). The overall PFS-12 rate was 25.4% (95% CI 9.8-51.7%; Q = 17.079, I^2 = 76.579, P = 0.002), overall OS-12 rate was 70.2% (95% CI 46.2-86.6%; Q = 13.260, I^2 = 69.834, P = 0.010), overall OS-24 rate was 37.2% (95% CI 15.9-64.8%; Q = 14.648, I^2 = 72.692, P = 0.005), and overall median OS was 11.212 months (95% CI 7.314-15.110 months; Q = 22.331, I^2 = 86.566, P < 0.001), as determined by the random-effects model. Incidence of grade 3-4 leukopenia and neutropenia was 20% and 6.8%, respectively. Fatal adverse effects were not reported. Conclusion: Combination therapy with interferon and TMZ is effective for HGG, although the available studies have several limitations.

Keywords: Combination therapy, interferon, temozolomide, high-grade glioma, meta-analysis

Introduction

Gliomas are the most common primary tumors of the central nervous system, with high-grade gliomas (HGG) accounting for approximately 80% of these tumors. Glioblastoma multiforme (GBM) with malignant features accounts for 50-60% of HGG cases. HGG may have low survival and high recurrence rates, significantly increasing therapeutic costs. Thus, treatment of HGG has been a clinical challenge. Currently, the clinical efficacy is still poor, with a median survival of only 14.4 months for GBM patients, even when advanced treatments are attempted [1].

For HGG, current guidelines recommend comprehensive treatment, including surgery, radiotherapy, and chemotherapy. Temozolomide (TMZ), a new imidazolyl tetrazide alkylating agent with anti-tumor activity, is the most common drug used for chemotherapy [1, 2]. TMZ administration is convenient with good tolerance. Moreover, the blood brain barrier is permeable to TMZ. In cells, TMZ can be degraded into potent alkylating agent, causing guanine alkylation, damaging the DNA and leading to tumor cell death [3]. However, with traditional 5-day TMZ-based chemotherapy, TMZ alone may induce drug resistance, causing treatment failure. Thus, it is imperative to develop economic and efficient chemotherapeutics that can be combined with TMZ to avoid drug resistance, increase the sensitivity of glioma cells to chemotherapeutics, and improve anti-tumor activity.

A large amount of evidence has shown that chromosome translocation (9; 11) (p22; q23) between Ets-1 and interferon (IFN) is a mechanism underlying the pathogenesis of human acute monocytic leukemia [4]. Activation of Ets-1 and type I IFN plays important roles in the pathogenesis of systemic lupus erythematosus [5, 6]. Effectiveness has been achieved in the clinical treatment of gliomas with IFN-α/β [7]. Thus, whether IFN with anti-angiogenic, immunoregulatory, and anti-tumor activities can be combined with TMZ to increase the clinical therapeutic efficacy of gliomas has become a hot topic in recent years [7, 8].

To date, several clinical trials have been conducted investigating the safety and efficacy of TMZ combined with IFN in the treatment of HGG. In this study, these clinical trials were systematically reviewed by meta-analysis, evaluating the overall clinical efficacy and safety of this treatment for HGG.

Methods

Literature search

The present systematic review and meta-analysis was performed according to PRISMA [9]. Two authors (DW and ZG), independently, searched Medline (via PubMed) and EMBASE databases, along with the Cochrane Library (up to September 12, 2017), to identify relevant studies. Human studies published in English were included. The following terms were used in the Medline search: [(Brain Neoplasms [Mesh]) OR (brain tumor*) OR (Glioma [Mesh])] AND (temozolomide OR temodar OR temodal) AND (Interferon OR Interferons) AND Humans [Mesh] AND English [Lang]. References for identified studies were checked manually to identify other potentially eligible trials. This procedure was performed iteratively until no additional studies could be included.

Inclusion criteria

Inclusion criteria were as follows. Clinical trials were designed to evaluate the overall efficacy of combination therapy with IFN and TMZ for HGG (AA, AO, AOA, or GBM) in adult patients (≥ 18 years old) with Karnofsky Performance Status scores (KPS) ≥ 60 and normal hematological, renal, and hepatic functions. Newly diagnosed or recurrent HGG were confirmed by histological examinations. Data concerning tumor response, progression-free survival (PFS), overall survival (OS), or adverse events were available.

Data extraction

Two investigators (DW and ZG), independently, extracted the following information: first author, year of publication, country, study design, IFN and TMZ dose and protocol, number of patients, participant characteristics, tumor response, follow-up of progression and survival, and adverse events. Extracted data were input into a standardized Excel (Microsoft Corp) file and checked by the other authors (MH, DF, FW, and HC). Any discrepancies were resolved by discussion. When progression or survival data were shown in Kaplan-Meier survival curves, diagrams were digitized to extract the values using Engauge Digitizer version 4.1 [10].

Clinical outcomes

Clinical outcomes included tumor response rate, 6-month PFS (PFS-6), 12-month PFS (PFS-12), median PFS, 12-month OS (OS-12), 24-month OS (OS-24), and median OS. The primary outcome was tumor response rate, which was widely accepted and most recorded. In addition, other outcomes, such as MGMT-positive rate and adverse events, were reported. Tumor response was recorded as [11, 12] complete response (CR), the disappearance of all radiographically measurable lesions, and no new lesions. Partial response (PR) included ≥ 50% reduction in the enhancing component of all brain lesions with no new lesions. Progressive disease (PD) included ≥ 25% increase in the enhancing tumor, the presence of new lesions, and failure to return for evaluation due to death or deterioration of disease condition. Stable disease (SD) encompassed all other situations.

Statistical analysis

Cochrane's *Q* statistic was computed to evaluate the heterogeneity of included trials. The assumption of homogeneity was considered to be effective if $P \geq 0.1$ [13] and a fixed-effects model was used. A random-effects model was chosen when $P < 0.1$. A two-tailed $P < 0.05$ indicates statistical significance. All statistical analyses were performed using Comprehensive

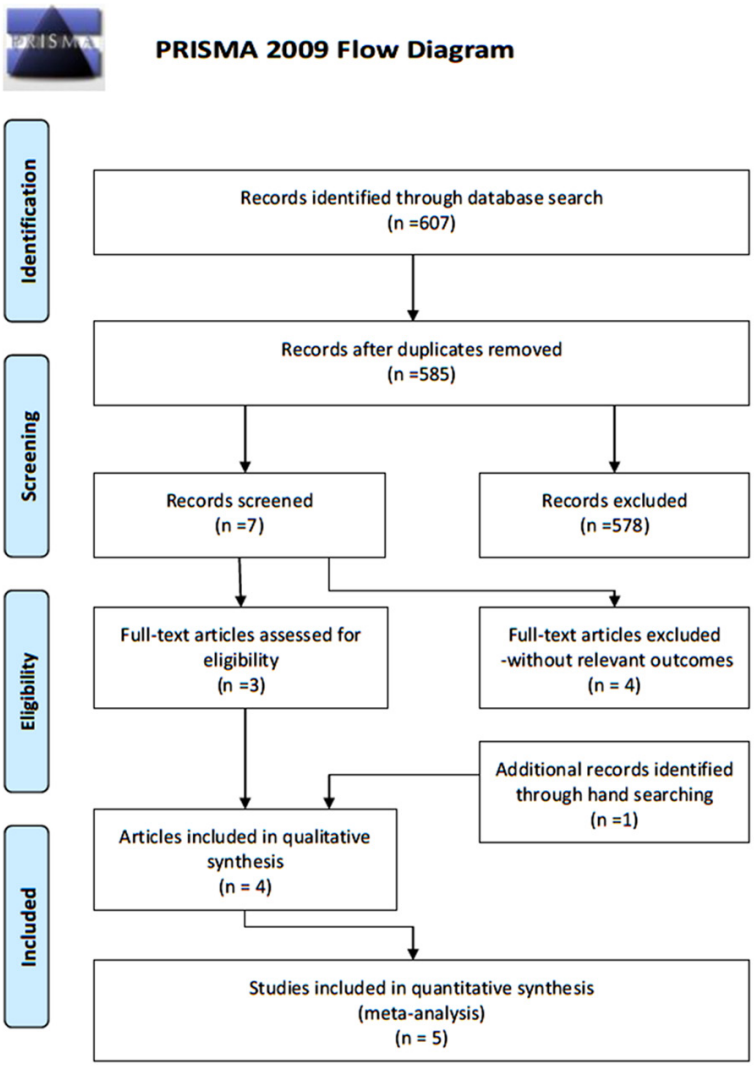

Figure 1. Flowchart of study inclusion for meta-analysis.

Meta-Analysis program version 2 (Biostat, Englewood, NJ, USA).

Results

Study identification

Figure 1 is a flowchart of study identification for the current meta-analysis. Twenty-two articles were excluded because of duplicate studies and 578 articles were excluded based on the titles and abstracts. The remaining seven articles [11, 14-19] were reviewed for more detailed evaluation. Four articles (one meeting abstract [14], one clinical trial note [19], and two case reports [15, 16]) were further excluded due to absence of relevant outcomes. Finally, the full-text article [20] of the meeting abstract was obtained by manual searching. Thus, four articles [11, 17, 18, 20], including five studies that met the inclusion criteria, were included in the present meta-analysis.

Study characteristics

Main characteristics of the studies included in the meta-analysis are provided in **Table 1**. A total of 155 patients (55 with newly diagnosed HGG and 100 with recurrent HGG) were included in these studies. The median age was 52.9 years (range: 12-84 years). The median KPS score ranged from 80 to 90. These five studies included three single-arm phase II clinical trials, one single-arm phase I clinical trial, and one retrospective study. Three studies were conducted in Asians and two studies in Americans. Two studies investigated grade III-IV gliomas, while three studies examined grade IV gliomas.

All five studies used the conventional standard 5-day TMZ protocol, in which TMZ was administered at 150-200 mg/m^2 for 5 consecutive days, once every 28 days per course. In Yang's study, patients were orally treated with 200 mg/m^2 TMZ on days 2 to 6, whereas INF-β 3 MIU was subcutaneously injected on days 1, 3, and 5 with a 4-week cycle until tumor progression or unacceptable toxicity [20]. In both Wakabayashi's and Motomura's studies, patients received 150 mg/m^2 TMZ on days 1-5 in the first cycle and 200 mg/m^2 TMZ on days 1-5 in the second to sixth cycle, whereas 3 MIU INF-β was administered intravenously on the first morning every 4 weeks [17, 18]. In two studies by Groves et al., 200 mg/m^2 TMZ was used for patients without prior chemotherapy or 150 mg/m^2 TMZ for patients with prior chemotherapy, whereas 4 MIU/m^2 IFN-α2b was subcutaneously injected for 3 days weekly

Table 1. Main characteristics and efficacy of clinical trials included in the meta-analysis

Study	Country	Trial design	Schedule	No patients enrolled (male, female)	Prior TMZ	Newly diagnosed	Relapse	Median age, year (range)	Median KPS	MGMT	
										(+)	(-)
Yang et al. 2012	China	Single-arm phase II	IFN-β 3 MIU/body IH. Days 1, 3, 5; TMZ 200 mg/m^2-d, days 2-6, q28	30 (23, 7)	Yes	0	30	44.5 (22-73)	80	16	14
Wakabayashi et al. 2011	Japan	Single-arm phase I	IFN-β 3 MIU/body IV; TMZ (150-200) mg/m^2 days 1-5, q28	23 (10, 13)	Not all	16	7	51 (29-70) (23*)	80	NA	NA
Motomura et al. 2011	Japan	Retrospective study	IFN-β 3 MIU/body IV; TMZ (150-200) mg/m^2 days1-5 q28	39/68 (41, 27)*	No	39	0	55 (12-84) (68*)	80	45 (68*)	23 (68*)
Groves et al. 2009	USA	Single-arm phase II	IFN 4 MIU/m^2 IH 3 days per week, TMZ (150-200) mg/m^2 days 1-5 q28	34 (25, 9)	No	0	34	55 (17-69)	80	NA	NA
Groves et al. 2009	USA	Single-arm phase II	PEG 0.5 mg/kg IH per week, TMZ (150-200) mg/m^2 days 1-5 q28	29 (16, 13)	No	0	29	56 (20-67)	90	NA	NA

TMZ: temozolomide; KPS: Karnofsky Performance Status Score; MGMT: O^6-methylguanine DNA methyltransferase. *Data counts when the sample size was studied.

Table 2. Therapeutic efficacy of clinical trials included in the meta-analysis

Study	Type	No. of patients	Tumor response			PFS-6 (%)	PFS-12 (%)	Median PFS, months (95% CI)	OS-12 (%)	OS-24 (%)	Median OS, months (95% CI)
			CR+PR	SD	PD						
Yang et al. 2012	Grade III	13	5	4	4	52.8	44.4#	10.0 (0.5-19.5)	83.8#	83.9#	NA
	Grade IV	17	5	10	2	23.5	NA	5.0 (3.0-7.0)	35.9#	8.2#	9.5 (7.7-11.3)
Wakabayashi et al. 2011	Grade III	6	6 (15*)	5 (15*)	4 (15*)	NA	NA	NA	82.9#	50.3#	NA
	Grade IV	10				NA	50	NA	60#	19.8#	17.1
Motomura et al. 2011	Grade IV	39	NA	NA	NA	NA	47	11.6	83.6	34.5	19.9 (15.3-24.5)
Groves et al. 2009 (IFN)	Grade IV	34	4	18	12	31 (29*)	3.53#	3.6 (3.0-6.3)	NA	NA	7.2 (5.3-10.6)
Groves et al. 2009 (PEG)	Grade IV	29	1	17	11	38 (26*)	3.71#	4.4 (2.4-6.5)	NA	NA	10.0 (7.8-14.3)

CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; PFS: progression-free survival; OS: overall survival; PEG: pegylated INF-α2b; #Engauge Digitizer 5.1 was employed to extract the values in the survival curve; *Sample size at final analysis.

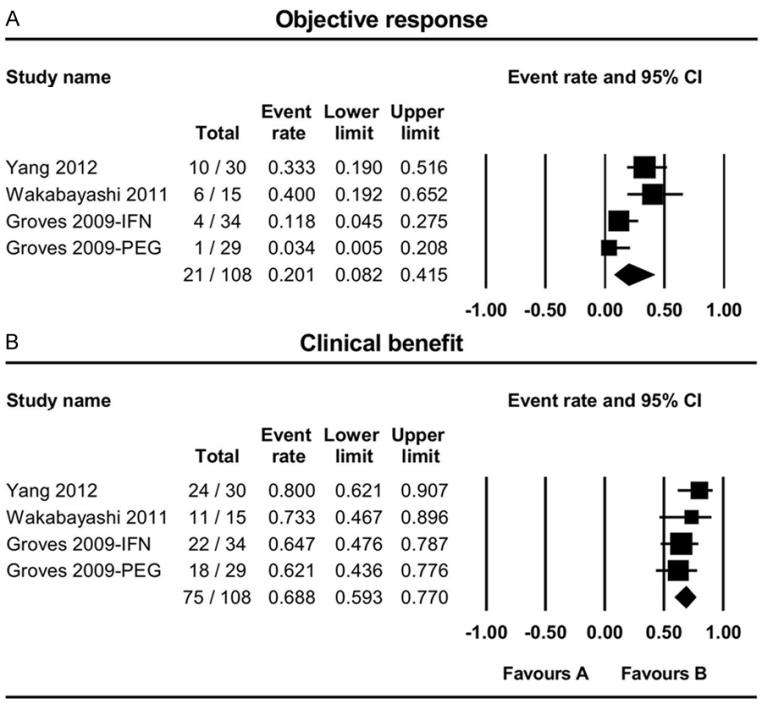

Figure 2. Total objective response (A) and total clinical benefit (B).

(Monday, Wednesday, Friday) on days 8 to 28 in each 28-day course. A total of 0.5 mg/kg PEG was administered subcutaneously every week [11].

Tumor response

The therapeutic efficacy of these clinical trials is shown in **Table 2**. As few HGG patients can achieve CR, the data on CR were not analyzed separately. Both objective response (CR and PR) rates and clinical benefit (CR, PR, and SD) rates were calculated. Objective response (OR) and clinical benefits (CB) were calculated for the 108 patients enrolled in four studies. The OR rate ranged from 3.4% to 40.0%. The overall OR rate was 20.1% (95% CI 8.2-41.5%; **Figure 2A**). Thus, a random-effects model was used (heterogeneity analysis: Q = 10.603, I^2 = 71.707, P = 0.014). The CB rate ranged from 62.1% to 80.0% and the overall CB rate was 68.8% (95% CI 59.3-77.0%; **Figure 2B**), as determined by the fixed-effects model (heterogeneity analysis: Q = 2.718, I^2 = 0.000, P = 0.437). To explore heterogeneity, tumor response was further analyzed according to the glioma grade. As shown in **Table 3**, there were no significant differences in CB (69.2% vs. 68.9%, P = 0.981) between grade III and grade IV gliomas. However, a trend favoring grade III glioma was noted according to the OR (38.3% vs. 13.5%, P = 0.098).

Progression-free survival

PFS was a major outcome in the study. PFS-6, PFS-12, and median PFS were analyzed, independently. PFS-6 was available in 85 patients enrolled in three studies. PFS-6 rates ranged between 23.5% and 52.8%, while the overall PFS-6 rate was 35.4% (95% CI 25.8-46.3%; **Figure 3A**), as determined by the fixed-effects model (heterogeneity analysis: Q = 2.995, I^2 = 0.000, P = 0.392). Further analysis to explore heterogeneity did not find significant differences in PFS-6 between grade III and grade IV gliomas (52.8% vs. 32.0%, P = 0.157, **Table 3**).

PFS-12 was available in 125 patients enrolled in five studies. PFS-12 rates ranged between 3.5% and 50.0%, while the overall PFS-12 rate was 25.4% (95% CI 9.8-51.7%; **Figure 3B**), as determined by a random-effects model (heterogeneity analysis: Q = 17.079, I^2 = 76.579, P = 0.002). Further analysis to explore heterogeneity did not find significant differences in PFS-12 between grade III and grade IV gliomas (44.4% vs. 19.3%, P = 0.219, **Table 3**).

In addition, median PFS was available in 132 patients enrolled in four studies. Median PFS ranged from 3.6 to 10.0 months, while the overall median PFS was 4.306 months (95% CI 3.231-5.380 months; **Figure 3C**), as determined by a fixed-effects model (heterogeneity analysis: Q = 2.554, I^2 = 0.000, P = 0.466). Further analysis to explore heterogeneity did not find significant differences in median PFS between grade III and grade IV gliomas (10.0 months vs. 4.232 months, P = 0.237, **Table 3**).

OS

OS-12, OS-24, and median OS were analyzed independently. Both OS-12 and OS-24 were available in 85 patients enrolled in three trials. OS-12 rates ranged between 35.9% and 83.8%,

Table 3. Various clinical outcomes between grade III and grade IV gliomas

	Objective response[1]		Clinical benefit[2]		PFS-6		PFS-12		Median PFS		OS-12		OS-24	
	n	Rate (%)	n	Rate (%)	n	Rate (%)	n	Rate (%)	n	Months	n	Rate (%)	n	Rate (%)
Overall	93	24.8	93	69.0	85	35.4	117	35.1	85	4.306	85	75.8	85	34.6
Grade III	13	38.5	13	69.2	13	52.8	13	44.4	19	10.000	19	83.5	19	70.3
Grade IV	80	13.5	80	68.9	72	32.0	104	19.3	66	4.232	66	62.4	66	22.5
P-value*		0.098		0.981		0.157		0.219		0.237		0.237		0.030

[1]Includes CR and PR. [2]Includes CR, PR and SD. *Between grade III and grade IV gliomas.

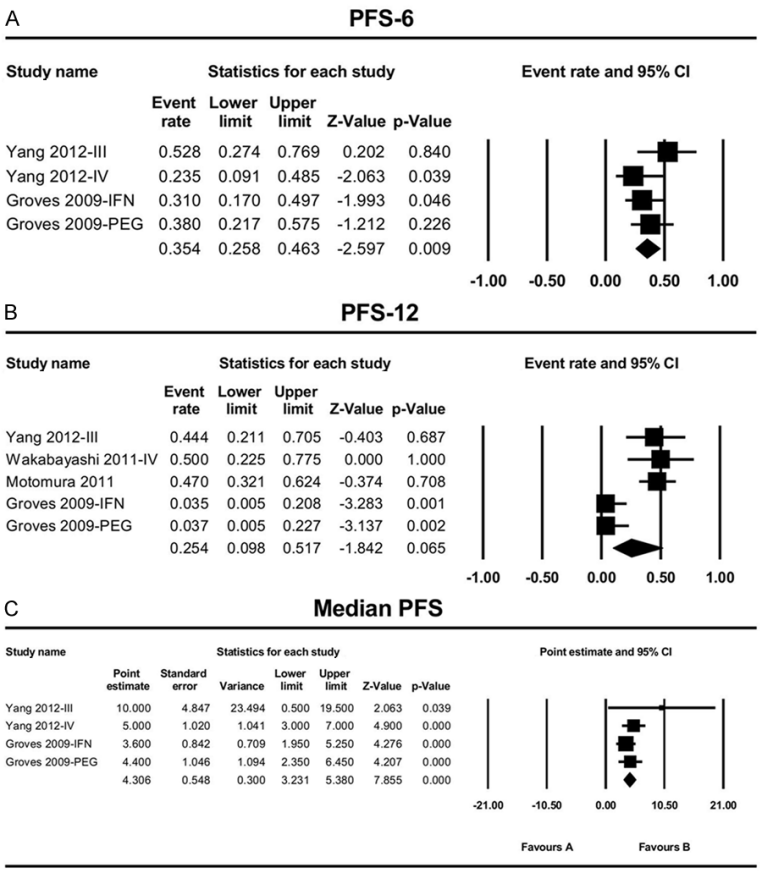

Figure 3. PFS-6 rate (A), PFS-12 rate (B), and median PFS (C).

with an overall OS-12 rate of 70.2% (95% CI 46.2-86.6%; **Figure 4A**), as determined by a random-effects model (heterogeneity analysis: Q = 13.260, I^2 = 69.834, P = 0.010). Further analysis to explore heterogeneity did not find significant differences in PFS-6 between grade III and grade IV gliomas (83.5% vs. 62.4%, P = 0.237, **Table 3**).

OS-24 rates ranged between 8.2% and 83.9%, while the overall OS-24 rate was 37.2% (95% CI 15.9-64.8%; **Figure 4B**), as determined by a random-effects model (heterogeneity analysis: Q = 14.648, I^2 = 72.692, P = 0.005). Further analysis to explore heterogeneity revealed significant differences in OS-24 between grade III and grade IV gliomas (70.3% vs. 22.5%, P = 0.030, **Table 3**).

In addition, median OS was available in 129 patients enrolled in five studies. Median OS ranged from 7.2 to 19.9 months, while the overall median OS was 11.212 months (95% CI 7.314-15.110 months; **Figure 4C**), as determined by a random-effects model (heterogeneity analysis: Q = 22.331, I^2 = 86.566, P < 0.001).

Other clinical outcomes

MGMT-positive rates were available in 91 patients enrolled in two trials. MGMT-positive rates ranged between 66.2% and 69.6%, while the overall MGMT-positive rate was 67.0% (95% CI 56.7-75.9%; **Figure 5**), as determined by a fixed-effects model (heterogeneity analysis: Q = 0.089, I^2 = 0.000, P = 0.765). Incidence of adverse events in included clinical trials is provided in **Table 4**.

Discussion

HGG includes grade III and grade IV gliomas, also known as malignant gliomas, according to the pathological classification of the World Health Organization. These tumors account for 80% of glioma cases and have high mortality and recurrence rates. Currently, therapeutic efficacy is poor for these tumors and treatment is costly. Thus, treatment of these tumors has been a clinical challenge. Available clinical guidelines recommend TMZ as the first line

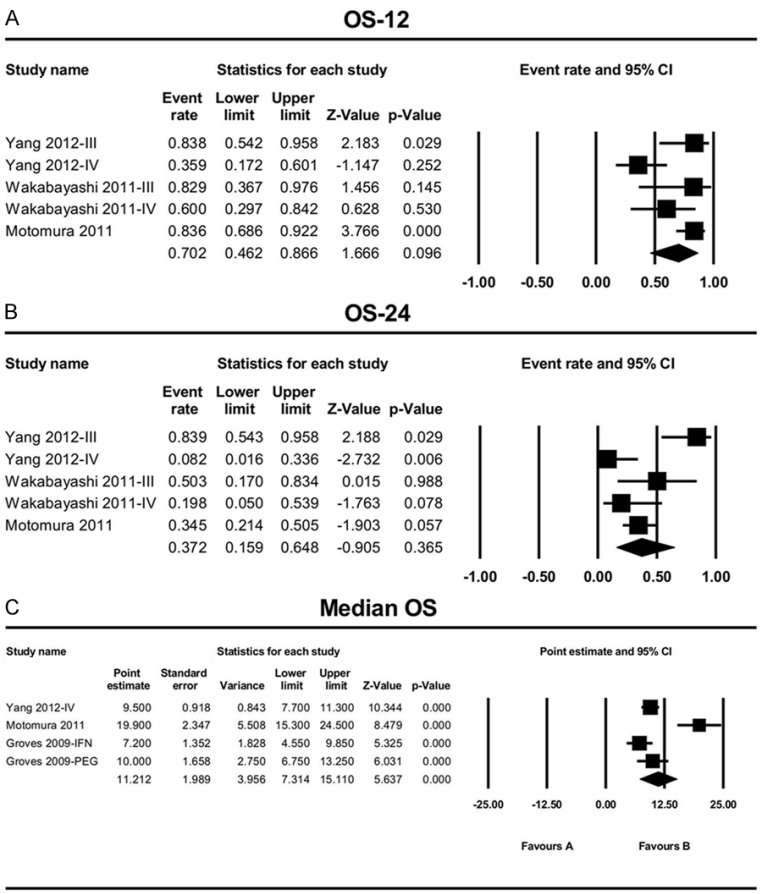

Figure 4. OS-12 rate (A), OS-24 rate (B), and median OS (c).

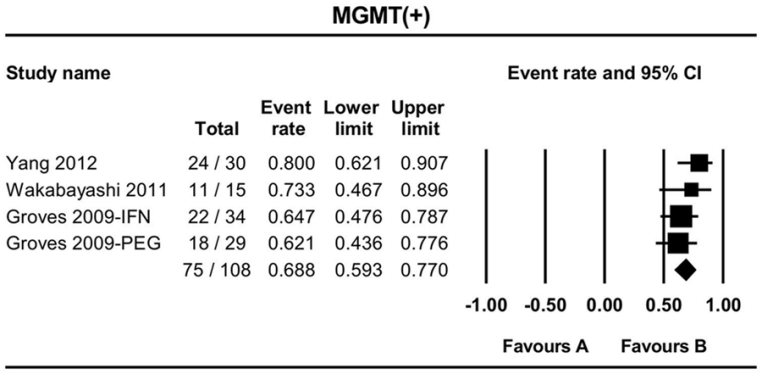

Figure 5. MGMT- positive rate.

chemotherapeutic in the treatment of HGG [1]. Studies have confirmed that elevated MGMT activity may cause resistance to TMZ, leading to treatment failure [21]. Thus, TMZ-based combination therapy has become a hot topic in the clinical treatment of HGG.

IFN is a type of cytokine widely used in clinical practice. It includes α, β, and γ subunits. It does not have anti-viral activity, but possesses anti-angiogenic, immunoregulatory, and anti-tumor activities. To date, IFN-α/β has been widely used in the clinical treatment of different malignant diseases, including gliomas [7]. In recent years, *in vitro* studies have revealed that IFN-α/β may reduce MGMT expression and activity, increasing the sensitivity of tumor cells to TMZ [14, 22, 23].

The current systemic review and meta-analysis evaluated the overall therapeutic efficacy and safety of combination therapy with IFN and TMZ in HGG. It was found that the OR was 20.1%, CB was 68.8%, median PFS was 4.31 months, and median OS was 11.21 months. These outcomes are comparable to those reported after other combination therapies [24-27]. Notably, this treatment is more convenient and economic, may not increase therapeutic costs, and may be more beneficial to patients.

In recent years, bevacizumab has been used clinically in TMZ-based combination therapy for newly diagnosed glioblastomas. The PFS improved, but OS was not significantly prolonged. Moreover, bevacizumab has serious adverse effects and is costly, significantly limiting its use [28, 29].

In addition, this study found that incidence of adverse events was low and incidence of grade 3-4 leukopenia and neutropenia was 20% and 6.8%, respectively. Fatal adverse effects were not reported. These adverse effects were resolved after symptomatic treatment, which did not affect subsequent treatments. There is evidence that the nitrosourea and PCV protocol may cause serious bone marrow suppression. The platinum-based protocol may cause gastrointestinal and kidney injury,

Table 4. Adverse events in clinical trials included in the meta-analysis

Adverse event	No. of patients	No. of trials	Rate (95% CI)	*Q* value	I^2 (%)	*P* value for heterogeneity
Grades 3-4 leukocytopenia	115	4	20.0% (7.5-43.5)	11.307	73.468	0.010
Grades 3-4 neutropenia	53	2	6.8% (0.9-36.5)	2.075	51.808	0.150
Grades 1-2 neutropenia	30	1	13.3% (5.1-30.6)	0.000	0.000	1.000
Grade 1 SGOT/SGPT elevation	53	2	17.4% (6.4-39.2)	2.223	55.006	0.136
Grade 1 fever	23	1	15.0% (5.3-35.7)	0.000	0.000	1.000
Thrombocytopenia	93	3	16.7% (10.3-25.9)	1.292	0.000	0.524
Nausea/vomiting	115	4	10.6% (3.4-28.6)	9.175	67.301	0.027
Fatigue	93	3	21.7% (14.5-31.3)	0.777	0.000	0.678

CI: confidence interval; SGOT/SGPT: serum aspartate aminotransferase/serum alanine aminotransferase.

irinotecan may induce fatal diarrhea, and bevacizumab has the risk of fatal intracranial hemorrhages and embolisms [30, 31], significantly compromising therapeutic efficacy.

There were limitations to the present analysis. First, only 155 patients were included in the final analysis. The small sample size limits the extension of these findings. Thus, more studies with large sample sizes are necessary to confirm the safety and clinical efficacy of combination therapy with IFN and TMZ for HGG. Second, both newly diagnosed HGG (n = 55) and recurrent HGG were included in the analysis (n = 100). This may be one reason for the shorter median OS (11.21 months), compared to combination therapy with bevacizumab (16 months [27], 16.8 months [28], 15.7 months [29]), as only newly diagnosed HGG patients were included in those studies.

Thus, it was hypothesized that there is an interaction between Ets-1 and IFN in the pathogenesis and clinical treatment of gliomas, while Ets-1 may be a target of IFN. However, whether the elevated efficacy of TMZ combined with IFN in the clinical treatment of HGG is related to this hypothesis and whether IFN-α/β induced reduction of MGMT expression is associated with Ets-1 requires confirmation from future studies.

Taken together, results of the current systemic review/meta-analysis show that combination therapy with TMZ and IFN is effective for HGG and the adverse effects are controllable. However, the available studies have some limitations. Thus, present results should be interpreted with caution. In the future, more clinical trials with larger sample sizes and basic research are needed to elucidate the advantages of combination therapy with IFN and TMZ for HGG.

In conclusion, combination therapy with IFN and TMZ is effective and safe for HGG. However, these results should be interpreted with caution given the various limitations. Further studies are needed to clarify optimal strategies for combination therapy for HGG.

Acknowledgements

This study was funded by the Chongqing Committee of Science and Technology, China (Grant No. cstc2016jcyjA0110).

Disclosure of conflict of interest

None.

Address correspondence to: Hai-Bin Chen, Department of Histology and Embryology, Shantou University Medical College, Shantou 515041, Guangdong Province, China. Tel: +86-754-88900297; Fax: +86-754-88550870; E-mail: chenhb@stu.edu.cn

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