Concomitant or adjuvant temozolomide with whole-brain irradiation for brain metastases: a meta-analysis

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The objective of this study was to assess the clinical efficacy and safety of concomitant or adjuvant tomozolomide with whole-brain irradiation (WBI) in patients with brain metastases. MEDLINE, EMBASE, Cochrane Library, Chinese Biomedical Literature Database were searched to identify relevant original published trails, and the references of eligible studies were manually screened. Randomized controlled trails reported in any language, comparing concomitant or adjuvant temozolomide (TMZ) and WBI with WBI alone in patients with brain metastases, were eligible for inclusion. Two investigators independently assessed the quality of included trials and extracted data. The RevMan 5 software was used for statistical analysis. Four trials involving 280 patients were included. The result showed that the group TMZ + WBI was superior to group WBI in partial response, stable disease, progressive disease, and objective response with the pooled risk ratio value and 95% confidence interval, respectively, 1.89 (1.19–3.02), 0.82 (0.45–1.50), 0.29 (0.10–0.78), and 1.72 (1.32–2.24). The incidence of gastrointestinal symptoms and ≥ grade 3 myelosuppression presented statistical difference, TMZ + WBI group is higher than WBI group, the pooled risk ratio value and 95% confidence interval were 3.75 (1.04–13.44) and 13 (1.75–96.79), respectively. The currently available evidence showed that the combination of TMZ and WBI may moderately improve the response rate, but accordingly increase the incidence of gastrointestinal symptoms and myelosuppression. Future large-scale, high-quality, placebo-controlled, double-blind trials are needed. *Anti-Cancer Drugs* 21:120–128 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Brain metastases (BMs) are the most common form of intracranial tumor in adults, which occur in approximately 25% of all cancer patients with metastatic disease and develop in approximately 40% of all cancer patients [1,2]. The most common primary tumors responsible for BMs are lung, breast, melanoma and unknown primary tumors [3]. Approximately half of all BMs occur because of lung cancer. More than 80% of BMs are detected after the primary tumor has been diagnosed [4]. In fact, the median overall survival (OS) of untreated patients is less than 3–6 months [5]. Often these patients have severe neurological symptoms with a decrease in survival and quality of life.

Although surgery and radiosurgery can produce effective palliation in selected cases, these modalities are usually restricted to patients with solitary lesions. Whole-brain irradiation (WBI) is considered standard treatment for the patients with multiple BMs. Data suggest that early WBI improves neurological control rate. As the average survival is 3–4 months in about 50% of BMs [6], many practitioners are inclined to defer WBI until the disease in the brain becomes symptomatic.

The role of systemic chemotherapy in the management of BMs is also limited and controversial [7]. Several studies of administering cisplatin and etoposide chemotherapy to patients with BMs suggested that the objective responses are rarely observed and the survival benefit is very rare, and that the incidence of neurological toxicity and myelosuppression increases [8,9]. Although the reported response rates range from 56 to 82% in BMs with primary cancer of the lung and breast [10], efficacy is determined by the sensitivity of tumor cells to chemotherapeutic agents and whether or not these drugs can cross the blood–brain barrier (BBB) [11]. Thus, the choice of chemotherapy regimen is often complicated by previous systemic treatments, and it is necessary to take into account the activity of the drugs in extracranial metastatic disease and the issue of drug concentration within the central nervous system (CNS).

Temozolomide (TMZ) is an oral alkylating agent that is rapidly absorbed (peak concentrations after 30–90 min), and penetrates into all body tissues including the CNS. It spontaneously converts into the active metabolite (MTIC), which is a reactive DNA methylating agent [12]. The cytotoxicity of MTIC is thought to be caused

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by methylation of the O^6 position of guanine [13]. The higher bioavailablity, crossing the BBB, and achieving effective concentrations in the CNS are considered as the superiorities of TMZ. Myelosuppression is the primary toxicity associated with TMZ, but it is reversible and noncumulative [14]. Single-agent TMZ achieved 41% disease control [partial response (PR) or stable disease (SD)] in patients with recurrent BMs with minimal toxicity [15]. Therefore, TMZ may be a reasonable treatment option for patients with BMs. An in vitro evaluation showed that a combination of TMZ with radiotherapy (RT) could enhance responsiveness, and has been proven to be the best modality [16]. Additionally, many clinical trials based on TMZ combined with WBI have shown that this modality for treating patients with newly diagnosed glioblastoma multiforme is reasonable and effective, not only for prolonging survival, but also for improving quality of life [16–18]. We conducted a meta-analysis to assess the effect of TMZ combined with WBI in patients with BMs.

Methods

Purpose

The purpose of this study was to investigate whether the administration of concomitant or adjuvant TMZ with WBI was effective or safe as combined treatment for patients with BMs, irrespective of cancer type.

Types of studies, participants, interventions, and outcome measures

All randomized controlled trials (RCTs), published and unpublished, which met the inclusion criteria, were eligible for this meta-analysis. All the trials compared concomitant TMZ with WBI versus WBI alone in patients with BMs (single or multiple sites). Patients with histologically proven BMs at the primary site (lung, breast, or melanoma) or from an unknown primary tumor assessable by contrast-enhanced computed tomographic scan or gadolinium-enhanced magnetic resonance imaging were the eligible participants. All patients were to receive WBI and the treatment group was to receive concomitant or adjuvant TMZ chemotherapy. TMZ was administrated orally at a dosage of 75 or 200 mg/m^2/day during the radiation treatment and 150–200 mg/m^2/day $\times$ 5 days every 28 days after WBI from the first treatment day continuing to disease progression or unacceptable toxicity. Planned conventional WBI was administrated with a total dose of 30–40 Gy in 10–20 fractions for 2–4 weeks.

Primary measurements were response rate (including complete response, PR, and objective response), SD, progressive disease (PD), and toxicity. Secondary outcomes included median survival and progression-free survival (PFS).

Complete response: disappearance of all known BMs. PR: 50% or greater decrease in measurable brain lesions or an objective improvement in evaluable brain lesions. SD: brain lesions unchanged ($< 50\%$ decrease or $< 25\%$ increase in the size of measurable lesions). PD: more than 25% increase in the size of some or all of brain lesions and/or the appearance of any new brain lesions [3]. PFS is defined as data on patients who were alive and free of disease progression and were censored at the time of the last follow-up visit.

Search strategy for the identification of studies

Medline (1966–June 2008), EMBASE (1974–June 2008), Cochrane Library (Issue 2, 2008), Chinese Biomedical Literature Database (1978–June 2008) were independently searched in duplicate to identify all published (manuscripts and abstracts) RCTs comparing concomitant or adjuvant TMZ and WBI with WBI alone for patients with BMs. Manual searches were done by reviewing articles and abstracts cited in the reference lists of identified RCTs. In addition, abstracts published in the Proceedings of the Annual Meetings of the American Society of Clinical Oncology (through 2008) were systematically searched for evidence relevant to this meta-analysis. There were no language and date restrictions. The following search terms were used: (Brain metastases, Intracranial metastases, Intracranial metastatic tumor) and (temozolomide, temodar) and (RT, irradiation, radiation therapy; radiotherapeutics) and (clinical trial phase III, randomized controlled trials). The searches were done by integrating Mesh heading [MEDLINE (MeSH), EMBASE (EMTREE)] and with text words. All the searched abstracts were screened for relevance. The selection of studies for inclusion was carried out independently by two authors.

Data extraction and quality assessment

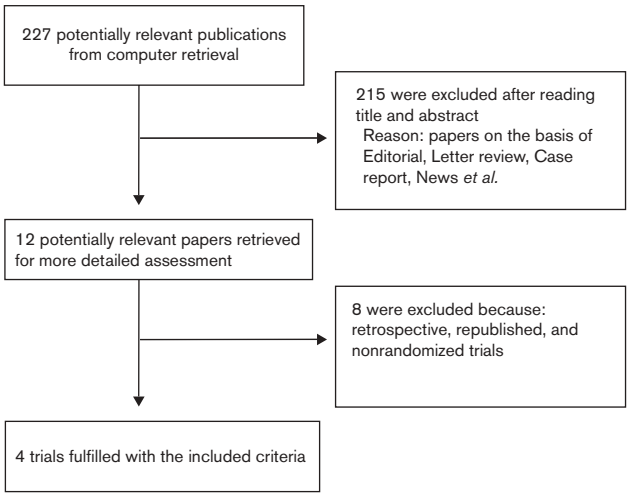
Data were extracted by two of us (Liu and Wang). The results were compared and disagreements resolved by consensus. Each study was evaluated for quality by two reviewers using the following Quality Assess Criteria of RCT: (i) randomized method, (ii) allocation concealment, (iii) blindness whether was adapted, (iv) with or without lost follow-up [if have been lost to follow-up, whether analysis in intention to treat] [19]. In the trials, where the four criteria were met, the quality of trials was highest and the possibility of bias was the smallest. If only a part of criteria were satisfied, the bias of trails was moderate. If none of criteria were satisfied, the bias was severe. In addition, we analyzed the baseline information and status of pathology and physiology of patients to judge the practice bias. If reviewers disagreed on the quality assessment, discrepancies were identified and a consensus was reached.

Statistical analysis of the review

We analyzed, extracted, and pooled data using Review Manager 5.0 for summary estimate [20]. We expressed results for dichotomous outcomes standard mean as

weighted risk ratios (RR) with 95% confidence intervals (CI). We used the χ^2 statistic to assess heterogeneity between trials and the I^2 statistic to assess the extent of inconsistency [21]. We used a fixed-effect model for calculations of summary estimates and their 95% CI, unless there was significant heterogeneity, in which case results were confirmed using a random-effects statistical model. Sensitivity analysis was performed by excluding the trials in which quality was very poor or there existed a significant clinical heterogeneity. Publication bias is a common concern in meta-analysis that is related to the tendency of journals to favor the publication of large and positive studies.

Fig. 1



Flowchart of studies selection.

Results

Description of trials

We obtained 227 potentially eligible publications after searching Medline etc., of which 215 articles were excluded after reading title and abstract. Fig. 1 showed the flowchart of the studies selection. Retrospective, republished, and nonrandomized trials were excluded. Eventually, the two reviewers agreed on the selection of four RCTs [22–25] involving 280 patients with mature results for meta-analyses. Table 1 [22–25] shows the characteristics of patients in the included trials.

Table 2 [22–25] shows the treatment characteristics. RT modalities varied between the trials in terms of total dose, dose per fraction, daily doses as well as duration of overall treatment. The Eugènia trial [22] and the Antonadou *et al.* trial [25] used total 30 Gy and 3×10 fractions during 2 weeks, but the Antonadou *et al.* trial [23] and Xie *et al.* trial [24] used a total of 40 Gy and 2×20 fractions in 4 weeks. Except the Xie *et al.* trial, the TMZ modalities were similar in the other three trials. Thus, there were no significant differences in main characteristics between treatment groups.

Methodological quality of included studies

Table 3 [22–25] contains specific information on study design. Each included RCT was assessed for quality using the validated Quality Assess Criteria of RCT [19].

Table 1 Characteristics of patients in the included trials

Study	Patients (T/C) (TMZ + WBI/WBI)	Range of age (years)	Primary tumor site			Brain metastases		Other organ metastases	Follow-up (months)
			Lung	Breast	Unknown	Solitary	Multiple		
Verger *et al.* [22]	41/41	≥ 18	42	13	27	No reported	No reported	56	October 2000 to August 2002
Antonadou *et al.* [23]	24/21	≥ 18	40	5	3	13	35	12	4
Xie *et al.* [24]	25/25	30–70	50			No reported	No reported	7	15.9
Antonadou *et al.* [25]	52/51	Unclear	103			No reported	No reported	Unclear	5.56

T/C, treatment group/controlled group; TMZ, temozolomide; WBI, whole-brain irradiation.

Table 2 Treatment characteristics of the trials

Trial	WBI total dose (Gy)	Number of fractions	WBI duration (weeks)	TMZ modalities	Patients	
					WBI + TMZ	WBI
Verger *et al.* [22]	30	10	3 Gy × 5 times/week × 2 week	75 mg/m^2/day × 5 days/week during RT + 200 mg/m^2/day × 5 day/28 days × 6 cycle	41	41
Antonadou *et al.* [23]	40	20	2 Gy × 5 times/week × 4 week	75 mg/m^2/day × 5 days/week during RT + 200 mg/m^2/day × 5 days/28 days × 6 cycle	24	21
Xie *et al.* [24]	40	20	2 Gy × 5 times/week × 4 week	200 mg/m^2/days × 5 days/28 days × n cycle from the first treatment day	25	25
Antonadou *et al.* [25]	30	10	3 Gy × 5 times/week × 2 week	75 mg/m^2/day × 5 days/week during RT + 200 mg/m^2/day × 5 days/28 days × 6 cycle	52	51

RT, radiotherapy; TMZ, termozolomide; WBI, whole-brain irradiation.

Table 3 The quality assessment of included studies

Study	Randomization method	Allocation concealment	Blinding	Lost to follow-up (no.)
Verger *et al.* [22]	Unclear	Unclear	Unclear	Yes (2)
Antonadou *et al.* [23]	Unclear	Unclear	Unclear	Yes (1)
Xie *et al.* [24]	Adequate	Unclear	Unclear	No
Antonadou *et al.* [25]	Unclear	Unclear	Unclear	No

Only one [24] of the four studies pointed out that randomization was done with envelope method. The other three studies did not specifically describe the randomization. Otherwise, the allocation concealment and blinding of four trials were all unclear.

Efficacy

Three trials [22–24] with 177 patients reported the CR rate as 16.7% (15 of 90) for TMZ + WBI group and 11.5% (10 of 87) for WBI group. The overall RR value and 95% CI was 1.36 (0.70–2.66). Tests for heterogeneity in the analysis were not significant ($P = 0.76$). CR rate was not statistically significant between TMZ + WBI arm and WBI alone arm with P value 0.37 (Fig. 2).

Three studies [22–24] representing a total of 177 patients reported PR rate, 37.8% (34 of 90) and 19.5% (17 of 87) for TMZ + WBI group and WBI group, respectively. The test for heterogeneity was not statistically significant ($P = 0.80$), allowing the results to be pooled with fixed-effects model. The overall RR value and 95% CI was 1.89 (1.19–3.02), which suggests that there was difference for PR rate between the TMZ + WBI and WBI alone group (Fig. 2).

The four include studies with 280 patients [22–25], which reported an OR rate. The OR rate was the sum of the CR rate and PR rate. The test for heterogeneity was not statistically significant with a P value 0.55, which indicates that the pooling of the data was valid. The OR rate was increased for TMZ + WBI (74 of 142 = 52.1%) compared with WBI alone (41 of 138 = 29.7%). The pooled RR value for all of the trials was 1.72 (95% CI: 1.32–2.24). The overall RR value suggested that there was a difference between the TMZ + WBI group and the WBI group in terms of OR with a P value less than 0.0001. TMZ + WBI group was superior to the WBI group in improving treatment response rate, reaching statistical significance (Fig. 2).

Three studies [22–24] with 177 patients reported SD. There was no statistical significance between TMZ + WBI group and WBI group, the pooled RR value was 0.82 (95% CI: 0.45–1.50). The test for heterogeneity was significant with a P value of 0.02. Repeated analyses of the above endpoints using random-effects model did not alter the results and conclusion (Fig. 2).

The effect of concomitant chemotherapy on response rate was displayed by PD. Three studies [22–24] with 177 patients had reported PD. There were more PD WBI (15 of 87 = 17.2%) compared with TMZ + WBI (four of 90 = 4.4%). The overall RR value was 0.29 (95% CI: 0.10–0.78). The test for heterogeneity was not significant with a P value of 0.92 (Fig. 2).

Toxicity evaluation

Nausea and vomiting were reported in three trials [22–24] involving 180 patients, 47.2% (43 of 91) for TMZ + WBI and 14.6% (13 of 89) for WBI. The random-effects model was used because of the heterogeneity ($I^2 = 72\%$, $P = 0.03$). Result showed there was a significant difference of gastrointestinal toxicity between TMZ + WBI and WBI alone with an RR value 3.75 (95% CI: 1.04–13.44) (Fig. 3).

Only two trials [22,25] reported $\geq$ grade 3 myelosuppression, and hematological adverse events and 132 patients were included. Meta-analysis indicated that there was a statistical difference between the TMZ + WBI group and the WBI group ($P = 0.01$), 18.2% (12 of 66) for TMZ + WBI group, and 0% (0 of 66) for the WBI group. The overall RR value was 13.0 (95% CI: 1.75–96.79). The test for heterogeneity was not significant with a P value of 0.62. One trial reported 40% (10 of 25) versus 26.1% (six of 23) in headache and 36% (nine of 25) versus 30.4% (seven of 23) in fatigue between the TMZ + WBI group and WBI group, but there was no statistical difference between them with P values of 0.32 and 0.68 (Fig. 4).

Survival

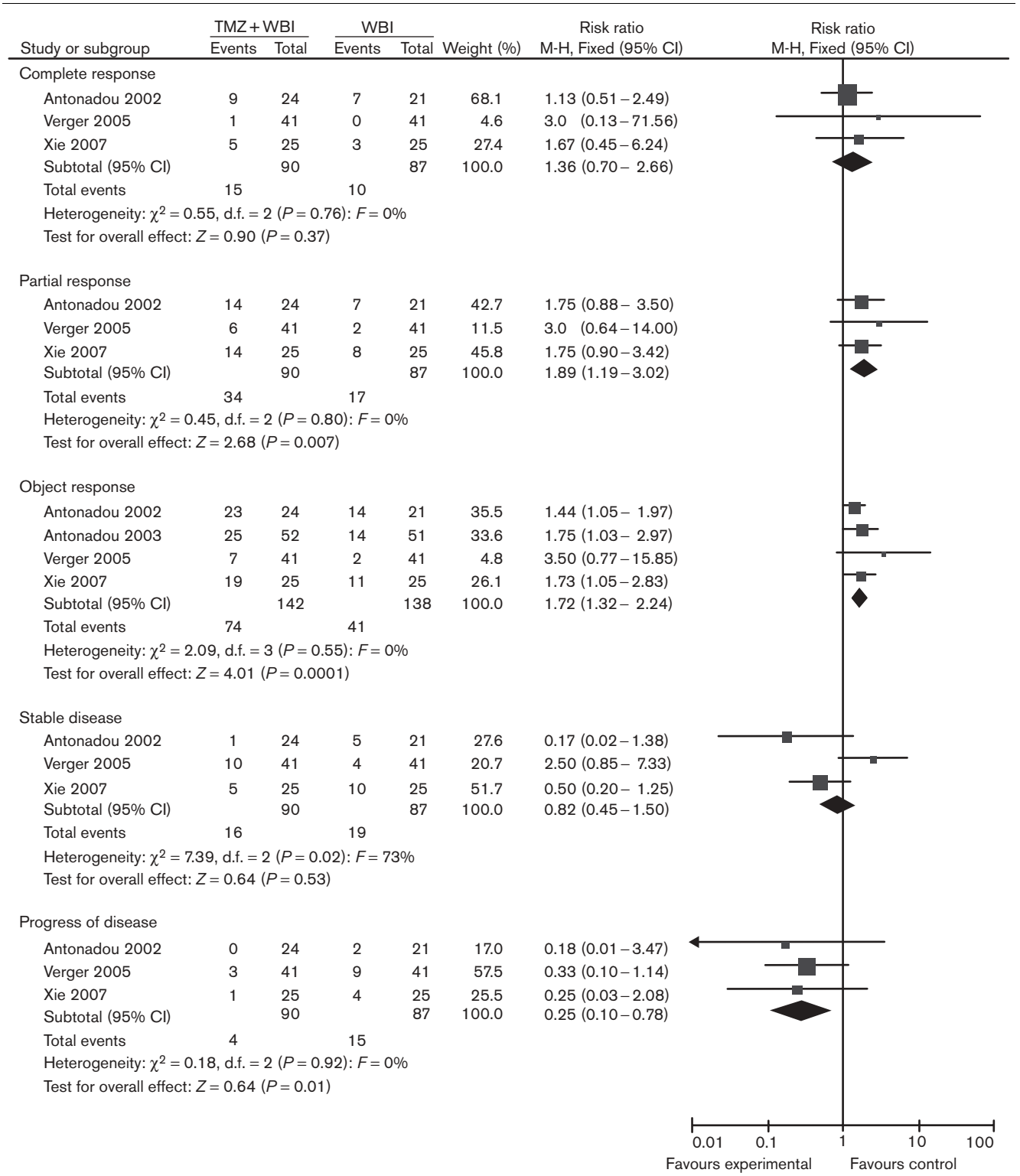
Only one trial with 82 patients reported the 3-month PFS, 73.2% (30 of 41) in TMZ + WBI group, and 53.7% (22 of 41) in WBI group [22]. There was no statistical difference between the two groups with a P value of 0.07 and an RR value of 1.36 (95% CI: 0.97–1.91). All four trials reported that the TMZ + WBI group was longer than the WBI group in median survival (4.5 vs. 3.1 months, 8.6 vs. 7.0 months, 8.6 vs. 4.5 months, and 7.9 vs. 4.3 months).

Discussion

TMZ crossed the BBB rather easily. It has recently been shown that TMZ has activity in patients with BMs from various malignancies. However, there has been limited experience with a combination of TMZ and WBI. Data from our meta-analyses confirm that concomitant or adjuvant TMZ chemoradiotherapy regimens provide substantial benefit for patients with BMs, mainly in terms of response rate. The results from all of the trials incorporating addition of TMZ to WBI show a statistically significant increase in the incidence of myelosuppression of grade 3 or more and hematological adverse events and symptoms of nausea and vomiting.

The activity and safety of TMZ as a single agent (using the standard 5-day dosing schedule) for the treatment of

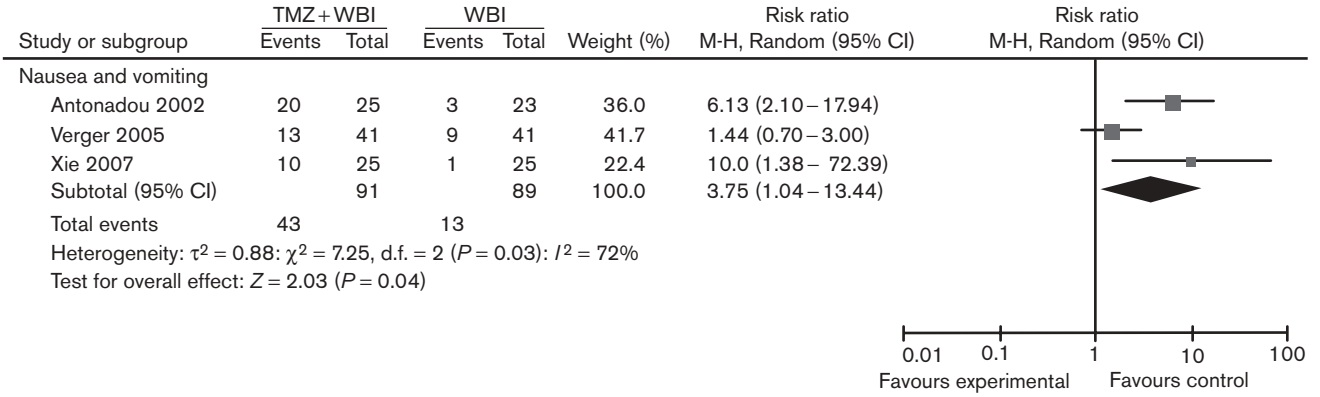
Fig. 2



Efficacy analysis of temozolomide (TMZ) + whole-brain irradiation (WBI) versus WBI alone in brain metastases. CI, confidence interval; d.f., degrees of freedom.

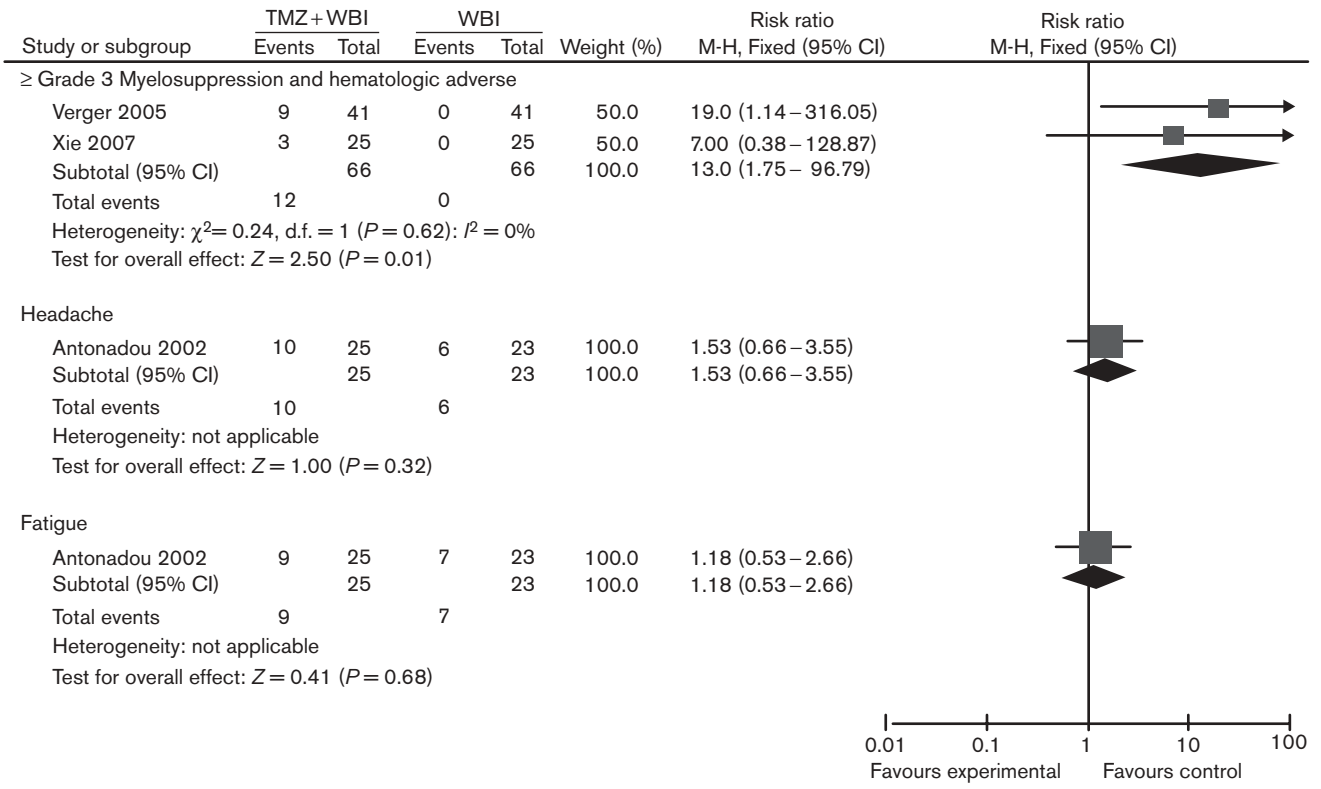
BMs, including patients with multiple brain lesions, were investigated in three phase II clinical trials. The OR rates were 7 and 5%, with minimal toxicity in two studies [15,26]. No objective response was observed in a study [27], which concluded lack of therapeutic activity of single-agent TMZ in patients with stage IV nonsmall-cell

Fig. 3



Comparison of gastrointestinal toxicity. CI, confidence interval; d.f., degrees of freedom; TMZ, temozolomide; WBI, whole-brain irradiation.

Fig. 4



Comparison of other adverse events. CI, confidence interval; d.f., degrees of freedom; TMZ, temozolomide; WBI, whole-brain irradiation.

lung cancer. All trials reported grade 3/4 hematological toxicity including thrombocytopenia, neutropenia, leucopenia, and nonhematological grade 3/4 adverse events including headache and vomiting. Three studies investigated the efficacy and safety of TMZ with concomitant WBI in patients with BMs; the OR rate was 57.6, 44, and 9.6% respectively [4,19,28]. From these clinical trials, it has been shown that TMZ administered as a single agent is modestly active and well tolerated. However, the trials of TMZ concomitant with WBI have provided optimistic information on the efficacy and safety. The combination of TMZ and WBI could usually achieve more effective antitumor activity with a 57.6% OR rate and median OS of 12 months for patients with BMs from solid tumors [28], but the patients with BMs from melanoma only showed very limited results [4,29]. This may be a chance

effect, but the other TMZ-based treatment options also showed similar conclusions [30–32]. In these studies, the OR rates were 36.8, 31.2, and 48%, respectively, with an acceptable side effect. Together, these data present a variety of effective TMZ-based treatment options for clinicians. The clinical studies evaluating the role of TMZ in patients with BMs have been mostly nonrandomized phase II trials. The results have been often divergent because of the variability in several factors, including tumor histology, presenting stage, previous use of chemotherapy, etc. The objective of our present meta-analysis based on four RCTs was to investigate the role of TMZ in addition to WBI for patients with BMs [22–25].

In our meta-analysis, the addition of TMZ to WBI in patients with BMs significantly improved the OR rate compared with WBI alone with the pooled RR value for all of the trials being 1.72 (95% CI: 1.32–2.24) and *P* value less than 0.0001. In one trial, the radiological response could only be assessed in 35 of 82 patients at 90 days; however, they analyzed the response rate according to the intention to treat. Patients without a radiological assessment at 90 days were considered to have had neurological progression. As a result, the combination of WBI plus TMZ did not increase the number of OR rate (17 vs. 5%) or OS and there were no statistical significant differences observed between the two groups with respect to response rate and PD. However, patients who were treated with TMZ + WBI had a longer PFS of BMs [22]. In three other RCTs, the OR rates were 96, 76, and 48%, respectively, in the TMZ + WBI group compared with 67, 44, and 27% in the WBI alone group, which was statistically significant [23–25].

In a large review of 1292 patients to define the prognostic factors in patients with BMs, Lagerwaard *et al.* [33] concluded that the three strongest prognostic factors were performance status, response to steroids, and evidence of systemic disease. Thus, the results of trials have often been divergent due to variability in several factors, including tumor histology, presenting stage, previous use of chemotherapy, etc. For clinical trials of combined-modality treatment with TMZ + WBI, these prognostic factors may be related to the difference of above outcomes. In the trial by Antonadou *et al.* [23], an OR rate of 96% was achieved with the combination of TMZ and WBI was substantially higher than in the other included trials. Despite the increased response rate, all patients received corticosteroids at the lowest dose necessary to maintain neurological stability before and during WBI. This unremarkable result needs to be further confirmed in a randomized trial.

Treatment modality may be a very critical factor influencing therapeutic effect. However, the Radiation Therapy Oncology Group has attempted to determine the optimal dose fractionation schedules for patients with BMs in many randomized trials [34,35]. All these trials have failed to show any benefit in survival for different doses and fractionation schedules of treatment. In our meta-analysis, 40 Gy in 20 fractions with two trials [23,24] seemed superior to 30 Gy in 10 fractions with respect to response rate [22,25]. However, this appearance was based on the concomitant or adjuvant TMZ. TMZ was administrated orally at a dosage of 75 mg/m^2/day during the radiation treatment and 200 mg/m^2/day $\times$ 5 days every 28 days after RT to patients for a maximum of six additional cycles in three trials [22,23,25], 200 mg/m^2/day $\times$ 5 days every 28 days from the first treatment day continuing to disease progression or unacceptable toxicity in the other trial [24]. This very small difference between treatment schedules is not statistically significant concerning response rate and toxicity. The tolerability of these dose-intensified schedules seemed suitable. One trial studied the prognosis affected by dose intensity of TMZ in patients with BMs from malignant melanoma, which indicated that increased dose intensity did not lead to a significant clinical benefit and prognosis [36]. A recent phase II trial using protracted low-dose TMZ and WBI for BMs tried to explore a new modality of this combined schedule. Low-dose TMZ was given at a dose of 75 mg/m^2 administered orally during RT, followed by 4 weeks off therapy and a subsequent TMZ administration at 75 mg/m^2 on days 1–21 every 4 weeks for up to 12 additional cycles. However, the results show that the combination of this new TMZ schedule and WBI is active and induces few side effects with the OR rate of 48.1% and without interruptions because of toxicity [37]. This suggested encouraging the design of additional schedules based on the combination of TMZ and other chemotherapeutic agents in the treatment of breast cancer and nonsmall-cell lung cancer, which are metastasis to brain.

Concomitant chemotherapy leads to higher toxicity than RT alone. Radiochemotherapy significantly increases the incidence of toxicity with a pooled RR value of 3.21 (95% CI: 1.84–5.60) and a *P* value less than 0.00001. Reported toxicological events were dose-limiting side effects such as nausea and vomiting. The risk of $\geq$ grade 3 myelosuppression and hematological toxicity was increased in two trials with a pooled RR value 13.0 (95% CI: 1.75–96.79) and a *P* value of 0.01 [22,24]. This was not observed in another two trials where WBI was combined with TMZ [23,25]. This probably reflects the more limited bone marrow reserve in patients who had received (76%) at least one treatment with chemotherapy before inclusion into the trial. Although cumulative myelosuppression is well documented, only mild to moderate myelosuppression (mainly thrombocytopenia) was completely reversible and resulted only in minor treatment delays up to 1 week. TMZ has an acceptable safety profile in patients with BMs. In one recent trial, even though it used a more intense dose of TMZ per cycle than any previous experience (1575 mg/m^2 compared with 750 mg/m^2), no serious toxicity was reported [37].

Our meta-analysis showed a significant improvement in response rate and trend towards improved survival in the TMZ + WBI arm (median survival 4.5 vs. 3.1 months, 8.6 vs. 7.0 months, 8.6 vs. 4.5 months, and 7.9 vs. 4.3 months, respectively, in four trials analyzed) [22–25]. They were not statistically significant. However, patients treated with TMZ + WBI had a slight improvement compared with WBI alone in survival. Furthermore, one trial reported the 3-month PFS, 73.2% (30 of 41) in the TMZ + WBI group and 53.7% (22 of 41) in the WBI group [22]. Although there was no statistical difference between the two groups with a *P* value of 0.07, it also supported the survival benefit of addition of TMZ to WBI. The efficacy and safety of TMZ administered concurrently with WBRT for patients with newly diagnosed BMs was also evaluated in recent trials. The largest of these trials demonstrated a significant improvement in the response rate and a trend toward improved survival in the combined therapy arm (8.3 vs. 6.3 months; *P* value of 0.179); however, it was not statistically significant [38]. These results are completely comparable with those of this study.

We have included one conference abstract that contained very limited data, which might impact the results of our study. Meta-analyses based on published data tend to overestimate treatment effects. In addition, the quality of all trials included was not high, the randomization, allocation concealment, and blinding of four trials were unclear. As only four trials were included in our analysis, publication bias was inevitable, and therefore we did not estimate publication bias with a 'funnel plot.' In our study, we included only four RCTs with 280 patients, which presented a sample size and inevitably declined the magnitude of conclusion. Most patients with BMs reluctantly underwent further comprehensive treatment to prolong very limit survival profit, but they usually chose alleviative treatment. Furthermore, because of the methodology defect of our meta-analysis, we cannot pool the median survival, a critical outcome of patients with malignancy. Therefore, on the basis of the above limitations, we should interpret the results with care, especially for a positive result. More high-quality RCTs involving unified treatment planning and larger samples need to be carried out to further validate the clinical efficacy and safety of this modality.

Conclusion

In conclusion, our analysis contained current available evidence showing that the combination of TMZ and WBI moderately improves the objective response and seems to prolong survival of patients with BMs. However, an increase of the incidence of gastrointestinal symptoms and myelosuppression is seen. Future large-scale, high-quality, placebo-controlled, double-blind trials are needed to confirm clinical efficacy and safety of the TMZ and WBI combination.

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