World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5306/wjco.v5.i1.19

World J Clin Oncol 2014 February 10; 5(1): 19-27
ISSN 2218-4333 (online)

REVIEW

Temozolomide for treatment of brain metastases: A review of 21 clinical trials

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Author contributions: Zhu W and Zhou L contributed equally to this work; Zhu W and Liu P designed the research; Zhu W, Zhou L, Qian JQ, Qiu TZ, Shu YQ and Liu P performed the research; Zhu W and Zhou L contributed new reagents/analytic tools, analyzed the data and wrote the paper.

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Received: September 7, 2013 Revised: November 2, 2013
Accepted: November 15, 2013
Published online: February 10, 2014

Abstract

Brain metastases from solid tumours are associated with poor prognosis despite aggressive treatment. Temozolomide can be used for the treatment of glioblastoma multiforme as well as melanoma. It has also been shown to have activity in patients with brain metastases from various malignancies, since it can cross the blood-brain barrier. To better understand the efficacy of temozolomide in the treatment of brain metastases, we carried out a review of 21 published clinical trials to determine whether temozolomide would benefit patients with brain metastases from solid tumours. Information regarding complete response, partial response, stable disease, objective response and objective response rate were collected to assess clinical outcomes. A modest therapeutic effect was observed when temozolomide was used as a single agent, however, the combination of temozolomide with whole-brain radiotherapy and/or other anticancer drugs exhibited encouraging activity. Thus, future high quality studies are warranted to confirm our findings.

Key words: Temozolomide; Solid tumours; Brain metastases; Clinical trials; Clinical outcomes

Core tip: Temozolomide has been used in glioblastoma multiforme as well as melanoma. Recently, studies showed that it might be also effective in patients with brain metastases from various malignancies. In this study, we carried out a review of 21 published clinical trials to determine whether temozolomide would benefit patients with brain metastases from solid tumours. As a result, a modest therapeutic effect was observed when temozolomide was used as a single agent, however, the combination of temozolomide with whole-brain radiotherapy and/or other anticancer drugs exhibited encouraging activity. This study for the first time provided a systematic evaluation of temozolomide in the treatment of brain metastases.

Zhu W, Zhou L, Qian JQ, Qiu TZ, Shu YQ, Liu P. Temozolomide for treatment of brain metastases: A review of 21 clinical trials. *World J Clin Oncol* 2013; 5(1): 19-27 Available from: URL: http://www.wjgnet.com/2218-4333/full/v5/i1/19.htm DOI: http://dx.doi.org/10.5306/wjco.v5.i1.19

INTRODUCTION

Brain metastases are a common complication in patients with cancer, occurring in approximately 25% of patients with disseminated diseases. The most common primary tumours, which metastasize to the brain, are lung cancer (25%-30%)[1,2], breast cancer (10%-15%)[3,4] and melanoma (12%-20%)[5]. Over two thirds of patients with brain metastases suffer debilitating neurologic symptoms, including headaches, focal weakness, cognitive dysfunction, and seizures. Prognosis in these patients is particularly

grim, and without treatment, median survival period is 1-2 mo, depending on the extent of cranial disease and the degree to which it can be controlled.

No standard systemic therapy exists for patients with brain metastases. Researchers continue looking for optimal treatments. Whole-brain radiotherapy was the standard of care in patients with multiple or inoperable brain metastases. Nevertheless, radiosurgery was becoming an increasingly attractive option for patients with up to four lesions[6,7], especially young patients with good performance status and satisfactory control of extra-cranial disease. Chemotherapy options were limited and generally used as salvage therapy in patients who failed to respond to whole-brain radiotherapy or radiosurgery[8,9]. However, the assumption that the blood-brain barrier prevented the passage of chemotherapy agents into the brain discouraged the use of systemic chemotherapy in treating brain metastases, even though the blood-brain barrier might already be disrupted by the presence of brain metastases and/or the treatment with whole-brain radiotherapy[10,11].

Temozolomide is an orally administered alkylating agent. It belongs to the imidazotetrazines and reaches the central nervous system in therapeutic concentrations. It can be rapidly absorbed following oral administration and undergoes spontaneous conversion at physiological pH to the active metabolite (3-methyltriazen-l-yl) imidazole-4-carboxamide in the tissues[12]. Clinical activity of temozolomide is closely linked to the activity of O6-alkylguanine-DNA alkyltransferase, a DNA repair protein which removes O6-alkylguanine adducts in DNA[13]. More importantly, temozolomide's ability to cross the blood-brain barrier has been demonstrated[14]. Temozolomide also has a good toxicity profile. The dose-limiting toxicity is non-cumulative myelosuppression that rarely requires treatment delay or dose reduction and may improve patients' life quality. Currently, temozolomide is a standard therapy in patients with refractory anaplastic astrocytomas. However, the optimal treatment of brain metastases is still under investigation. Theoretically, an efficacious and well-tolerated chemotherapeutic, such as temozolomide, might also show great potential to treat brain metastases. Therefore, we carried out a review of published clinical trials to better understand the efficacy of temozolomide in the treatment of brain metastases from solid tumours.

IDENTIFICATION OF ELIGIBLE STUDIES

We searched the PubMed database (until 5 April 2012) for the relevant articles by using the term "Temozolomide" with no limitations. In addition, another search strategy was employed by using the key term "Temozolomide", limited to "Humans", "Clinical Trial" and "Cancer". All relevant publications were reviewed and repetitive articles were eliminated. The articles in reference lists were also hand-searched for potentially relevant publications.

INCLUSION CRITERIA

All human-associated studies, regardless of tumour type, were included once they met the following criteria: (1) solid tumour with brain metastases (except primary brain tumour); (2) monotherapy or combination therapy with temozolomide; (3) histological confirmation; (4) relatively stable administration dosage of temozolomide; and (5) sufficient data of clinical outcomes.

DATA EXTRACTION

For each study, the following information was collected: first author, year of publication, country of the first author, the number of total and evaluable patients, median age, gender, cancer type, prior treatment, name of drugs, dose regimen, median cycle of treatment, clinical outcomes including the number of patients who achieved complete response, partial response, stable disease, objective response and progressive disease. For studies including different types of tumour, data were separately extracted by tumour type if information was enough.

LITERATURE SEARCH

A total of 2448 articles were identified from the PubMed database, of which 1987 were excluded due to repeated and unrelated contents. Among the rest, phase I studies were excluded as the administration dosage of temozolomide was not relatively stable. In addition, only trials on solid tumours with brain metastases were included in this review. Therefore, 21 papers were chosen from the remaining 461 articles for this study. Among these 21 articles, seven used temozolomide as a single agent while the others combined temozolomide with other anti-tumour drugs and/or radiotherapy.

Because of the heterogeneity of patients, regimens, clinical settings and a variety of outcome measurement in these trials, conducting a meta-analysis was inappropriate. Results were therefore analyzed qualitatively.

STUDY CHARACTERISTICS

Study characteristics information was summarized in Tables 1 and 2. Among all first authors, seven were from United States, five from Greece, four from Italy, two from Germany and one from each of United Kingdom, France, and Poland. The number of patients in these trials ranged from 11 to 157, with median age from 48 to 66. There were 12 cancer types described in these 21 trials, including non-small cell lung cancer, breast cancer, melanoma, small cell lung cancer, colorectal cancer, ovarian cancer, endometrial cancer, oral cavity cancer, renal cancer, bladder cancer, gastric cancer and carcinoma of the head and neck. Besides, there were five studies including unknown primary tumours. Most patients had received prior therapies and had metastatic or recurrent diseases at baseline.

TREATMENT ADMINISTRATION

In Tables 3 and 4, treatment administration information for each therapy type was recorded. In trials of mono-

Table 1 Study characteristics of the studies that used temozolomide as a single agent

Trial	Publication information (author/yr/country)	Patient characteristic			Cancer	Prior treatment
		Total number	Median age	Gender (male/female)		
1	Abrey *et al*[16]/2001/United States	41 (34[1])	60	11/30	NSCLC (*n* = 22) Breast (*n* = 10) Melanoma (*n* = 3) SCLC (*n* = 2) Rectal (*n* = 2) Ovarian (*n* = 1) Endometrial (*n* = 1)	WBRT (*n* = 41) Stereotactic RT (*n* = 9) Chemotherapy (*n* = 35) Surgery (*n* = 11)
2	Siena *et al*[20]/2009/Italy	157	51.1[4]/53.9[3]/59.1[2]	72/85	Melanoma (*n* = 53) Breast cancer (*n* = 51) NSCLC (*n* = 53)	WBRT (*n* = 41) Chemotherapy (*n* = 98) Radiotherapy (*n* = 34)
3	Schadendorf *et al*[21]/2006/Germany	45 (40[5]/37[6])	54.5	29/16	Melanoma	Chemotherapy (*n* = 21)
4	Giorgio *et al*[19]/2005/Italy	30	65	23/7	NSCLC	WBRT (*n* = 30) Stereotactic radio surgery (*n* = 1) Chemotherapy (*n* = 30)
5	Christodoulou *et al*[17]/2000/Greece	28 (24[1])	56	19/9	NSCLC (*n* = 12) SCLC (*n* = 5) Breast (*n* = 4) Other (*n* = 7)	WBRT (*n* = 23) Radiation(other sites) (*n* = 5) Surgery (*n* = 4) Chemotherapy (*n* = 22) Biologic therapy(*n* = 1)
6	Agarwala *et al*[15]/2004/United States	151 (122[1])	53[7]/46.5[8]	95/56	Melanoma	Chemotherapy (*n* = 34) Immunotherapy (*n* = 23[7]/21[8])
7	Dziadziuszko *et al*[18]/2003/Poland	12 (11[1])	57	6/6	NSCLC	WBRT (*n* = 4) Chemotherapy (*n* = 1) Surgery (NA) Radiotherapy (NA)

[1]The number of patients eligible for the assessment of clinical outcomes; [2]Non–small cell lung cancer (NSCLC); [3]Breast cancer; [4]Melanoma; [5]The number of patients eligible for the assessment of brain lesion response; [6]The number of patients eligible for the assessment of extracerebral response; [7]No prior chemotherapy; [8]Prior chemotherapy. NA: Not available; SCLC: Small cell lung cancer; WBRT: Whole-brain radiotherapy.

therapy, temozolomide was administered at a dose of 150-200 mg/m^2 per day on days 1-5 of a 28-d cycle[15-19] or 125-150 mg/m^2 per day on days 1-7, 15-21 of a 28- or 35-d cycle[20,21]. The median cycle of each treatment is summarized in Tables 1 and 3.

In trials that combined temozolomide with radiotherapy, patients were treated as follows: (1) 30 Gy of whole-brain radiotherapy with concomitant temozolomide (75 mg/m^2 per day) for 10 d, and subsequent temozolomide at a dose of 75 mg/m^2 per day for 21 d every 4 wk [22]; (2) A total dose of 30 Gy with ten daily fractions of 3.0 Gy was given 5 d per week over 2 wk, and temozolomide was administered at a dose of 95 mg/m^2 per day for the entire radiation treatment duration including days without radiation treatment[23]; (3) temozolomide was given at 60 mg/m^2 per day (days 1-16) concomitantly with whole-brain radiotherapy (36 Gy/12 fractions given in 16 d), and subsequent temozolomide at a dose of 200 mg/m^2 per day for 5 consecutive days every 28 d[24]; (4) temozolomide was given at 200 mg/m^2 per day on days 1-5 every 28 d. This therapy regimen was combined with stereotactic radiotherapy (20 Gy) or whole-brain radiotherapy (30 Gy)[25]; and (5) temozolomide was administered at a dose of 75 mg/m^2 per day concurrent with 40 Gy fractionated conventional external-beam radiotherapy (2 Gy, 5 d/wk) for 4 wk, and subsequent temozolomide at a dose of 200 mg/m^2 per day for 5 consecutive days every 28 d[26].

Among those studies that combined temozolomide with other drugs and radiotherapy or with other drugs alone, three added cisplatin[17,27,28], two combined thalidomide[29,30], and the rest used vinorelbine[31], lomustine[32], doxorubicin[33], arsenic trioxide[34] or docetaxel[27] as a part of chemotherapy protocol or radiation. The median cycle of each treatment is summarized in Tables 2 and 4.

CLINICAL OUTCOMES

Response criteria were used as defined by World Health Organization criteria, response evaluation criteria in solid tumors criteria, Macdonald criteria, Eastern Cooperative Oncology Group criteria or Standard response criteria. Objective response was based on the total number of patients who achieved complete response or partial response. Objective response rate was defined as the proportion of patients who got complete response or partial response. There were seven studies mentioning extracerebral or global responses as an endpoint[17,21,25,27,28,30,32]. The extracerebral and global objective response rates ranged from 0.027 to 0.291, and 0.088 to 0.428, respectively. Seventeen trials evaluated cerebral response. Interestingly, efficacy of monotherapy and combination therapy was

Table 2 Study characteristics of the studies that combined temozolomide with radiotherapy and/or other agents

Trial	Publication information (author/yr/country)	Patient characteristic			Cancer	Prior treatment
		Total number	Median age	Gender (male/female)		
8	Addeo *et al*[22]/2008/Italy	27	55	13/14	NSCLC (*n* = 15) Breast (*n* = 12)	Chemotherapy (*n* = 20) Surgery (*n* = 20) Radiotherapy (*n* = 12)
9	Mikkelsen *et al*[23]/2010/United States	17	65.4	10/7	Lung (*n* = 13) Colon (*n*=1) Melanoma (*n* = 1) Mixed (prostate, bladder, lung) (*n* = 1) Unknown (probably lung) (*n* = 1)	Chemotherapy (*n* = 7) Surgery (*n* = 1) Stereotactic radiosurgery (*n* = 2)
10	Kouvaris *et al*[24]/2007/Greece	33	66	22/11	SCLC (*n* = 4) NSCLC (*n* = 10) Breast (*n* = 7) Rectal (*n* =5) Melanoma (*n* = 5) Oral cavity (*n* = 1) Unknown (*n* = 1)	NA
11	Hofmann *et al*[25]/2006/Germany	35 (34[1])	53	19/16	Melanoma	Chemotherapy (*n* = 7) Immunotherapy (*n* = 4) Chemoimmunotherapy (*n* = 3) Surgery/radiosurgery (*n* = 4)
12	Antonadou *et al*[26]/2002/Greece	25 (24[1])	49	25/14	Melanoma	NA
13	Atkins *et al*[29]/2008/United States	39	61	29/10	Melanoma	Immunotherapy (*n* = 12) Radiotherapy (*n* = 7)
14	Cortot *et al*[28]/2006/France	50 (47[2]/33[3]/47[4])	57	40/10	NSCLC	Surgery (*n* = 40) Radiotherapy (*n* = 3)
15	Iwamoto *et al*[31]/2007/United States	38 (36[1])	57	15/23	NSCLC (*n* = 17) SCLC (*n* = 3) Breast (*n* = 11) Colon (*n* = 2) Renal (*n* = 2) Endometrial (*n* = 1) Bladder (*n* = 1) Head and neck (*n* = 1)	Chemotherapy (*n* = 37) WBRT (*n* = 30) Surgery (*n* = 20) Stereotactic radiosurgery (*n* = 18)
16	Larkin *et al*[32]/2006/United Kingdom	26 (14[1])	50	14/12	Melanoma	Immunotherapy (*n* = 7) Radiosurgery (*n* = 1) Surgery (*n* = 1)
17	Caraglia *et al*[33]/2005/Italy	19	63	7/12	Breast (*n* = 8) NSCLC (*n* = 6) Colo-rectal (*n* = 3) Melanoma (*n* = 1) Ovarian (*n* = 1)	Systemic treatment (*n* = 12) Radiotherapy(out of brain) (*n* = 3) WBRT (*n* = 13)
18	Bael *et al*[34]/2007/United States	11 (5[1])	50	8/3	Melanoma	Immunotherapy (*n* = 3)
19	Christodoulou *et al*[35]/2005/Greece	32 (21[1])	53	11/21	Breast (*n* = 15) NSCLC (*n* = 11) SCLC (*n* = 1) Gastric (*n* = 1) Melanoma (*n* = 3) Unknown (*n* = 1)	Chemotherapy (*n* = 27) Radiotherapy (*n* = 17) Surgery (*n* = 1)
20	Hwu *et al*[30]/2005/United States	26 (14[2]/15[3])	60	14/12	Melanoma	WBRT (*n* = 8) Stereotactic radiosurgery (*n* = 4) Surgery (*n* = 4)
21	Bafaloukos *et al*[27]/2004/Greece	25 (24[1])	48	15/10	Melanoma	NA

[1]The number of patients eligible for the assessment of clinical outcomes; [2]The number of patients eligible for the assessment of brain lesion response; [3]The number of patients eligible for the assessment of extracerebral response; [4]The number of patients eligible for the assessment of global response. TMZ: Temozolomide; NA: Not available; NSCLC: Non–small cell lung cancer; WBRT: Whole-brain radiotherapy.

quite different among these studies.

Out of the seven trials using temozolomide as a single agent and cerebral response as an endpoint, objective responses were observed in six studies with objective response rates ranging from 0.042 to 0.1. In the trial conducted by Giorgio *et al*[19], a total of 30 patients who had brain metastases from non-small cell lung cancer were included, and 2 patients got complete response, 1 partial

Table 3 Treatment administration and clinical outcomes of the studies that used temozolomide as a single agent

Trial	Cancer	Treatment administration			Clinical outcomes						
		Drug	Dose regimen	Median cycles	CR	PR	OR	ORR	SD	PD	Other (median[1])
1	NSCLC (n = 22) Breast (n = 10) Melanoma (n = 3) SCLC (n = 2) Rectal (n = 2) Ovarian (n = 1) Endometrial (n = 1)	TMZ	150-200 mg/m^2 per day, days 1-5/28-d cycle	NA	0	2[2]	2	0.059	15 (8[2]/4[3]/3[4])	17 (9[2]/3[3]/5[4])	TTP: 1.97 mo OS: 6.62 mo
2	Melanoma (n = 53) Breast cancer (n = 51) NSCLC (n = 53)	TMZ	150 mg/m^2 per day, days 1-7, 15-21/28- or 35-d cycle	NA	1[2]	9 (5[5]/2[3]/2[2])	10	0.064	31 (12[5]/8[3]/11[2])	116 (36[5]/41[3]/39[2])	PFS: 56 d[5]/58 d[3]/66 d[2] OS: 100 d[5]/172 d[2]
3	Melanoma	TMZ	125-150 mg/m^2 per day, days 1-7, 15-21/28-d cycle	48 d	0/0[6]	2/1[6]	2/1[6]	0.044/0.027[6]	5/5[6]	33/31[6]	OS: 4.1 mo (3.6 mo[8]/4.3 mo[7])
4	NSCLC	TMZ	150-200 mg/m^2 per day, days 1-5/28-d cycle	6	2	1	3	0.1	3	24	TTP: 3.6 mo OS: 6 mo
5	NSCLC (n = 12) SCLC (n = 5) Breast (n = 4) Other (n = 7)	TMZ	150 mg/m^2 per day, days 1-5/28-d cycle	NA	0	1	1	0.042	4	19	TTP: 3 mo OS: 4.5 mo
6	Melanoma	TMZ	150-200 mg/m^2 per day, days 1-5/28-d cycle	NA	1	8	9	0.074	40	73	PFS: 1.2 mo[7]/1.0 mo[8] OS: 3.5 mo[7]/2.2 mo[8]
7	NSCLC	TMZ	200 mg/m^2 per day , days 1-5/28-d cycle	1	0	0	0	0	3	8	NA

[1]Median: Data here are median values; [2]NSCLC; [3]Breast cancer; [4]Other cancer; [5]Melanoma; [6]Extracerebral response; [7]No prior chemotherapy; [8]Prior chemotherapy. TMZ: Temozolomide; NA: Not available; NSCLC: Non–small cell lung cancer; SCLC: Small cell lung cancer; SD: Stable disease; PR: Partial response; CR: Complete response; OR: Objective response; ORR: Objective response rate; PD: Progressive disease; PFS: Progression-free survival; TTP: Time to progression; OS: Overall survival.

response, and 3 stable disease. However, in another study of advanced non-small cell lung cancer with brain metastases[18], no objective response was achieved.

In trials that used combination therapy, objective response was observed in all studies with objective response rates greater than 0.1 except two studies. One trial evaluated vinorelbine and intensive temozolomide in patients with recurrent or progressive brain metastases with an objective response rate of 0.055[31]. Another one was temozolomide, thalidomide, and whole brain radiation therapy for patients with brain metastasis from metastatic melanoma with an objective response rate of 0.077[29]. The highest objective response rate in trials that combined temozolomide with radiotherapy was 0.959, achieved in the study of temozolomide and concurrent radiotherapy in patients with brain metastases from advanced lung cancer and breast cancer[26]. Whereas, in the trial of concurrent temozolomide and whole brain radiation therapy for multiple brain metastases which was conducted by Mikkelsen *et al*[23], objective response rate was 0.176 with 3 patients achieving partial response. In two studies that combined temozolomide with other drugs and radiotherapy, objective response rates were 0.077[29] and 0.128[28]. Among those studies that used combination chemotherapy, the highest objective response rate was observed in the trial of temozolomide plus pegylated liposomal doxorubicin in the treatment of brain metastases from solid tumours[35,36]. Stable disease was achieved in all studies. Other evaluation data, such as median overall survival, progression-free survival and time to progression, were also collected, if available and summarized in Tables 1-4.

DISCUSSION

Brain metastases from solid tumours are associated with poor prognosis despite aggressive treatment. Also, the majority of patients have suffered debilitating neurological symptoms. Standard systemic therapy for patients with brain metastases is still under investigation. However, many clinical investigations had been discouraged by the concern that although chemotherapy drugs would have efficacy against the primary tumour (*e.g.*, lung cancer), they would not cross the blood-brain barrier. Therefore, chemotherapy would not be active against the metastatic brain disease. Even though data suggested that the blood-brain barrier was disrupted when brain metastases were present and chemotherapy could be effective against brain metastases from chemosensitive solid tumours[37], unfortunately, the severe adverse events would be very difficult for pre-treated patients who had already received radiation and multiple regimens of myelosuppressive chemotherapy to tolerate. Temozolomide, a derivative of imidazotetrazine, is the prodrug of 3-methyl-(triazen-1-yl) imidazole-4-carboxamide. The therapeutic benefit of temozolomide depends on its ability to alkylate/methylate DNA, which most often occurs at the N-7 or O-6 positions of guanine residues. This methylation

Table 4 Treatment administration and clinical outcomes of the studies that combined temozolomide with radiotherapy and/or other agents

Trial	Cancer	Treatment administration			Clinical outcomes						
		Drug	Dose regimen	Median cycles	CR	PR	OR	ORR	SD	PD	Other (Median[1])
8	NSCLC (n = 15) Breast (n = 12)	TMZ, WBRT	WBRT 30 Gy, TMZ 75 mg/m^2 per day, days 1-10; subsequent TMZ 75 mg/m^2 per day, days 1-21/28-d cycle	4.2	2 (1[2]/1[3])	11 (5[2]/6[3])	13	0.481	6 (3[2]/3[3])	8 (6[2]/2[3])	PFS: 6 mo OS: 8.8 mo
9	Lung (n = 13) Colon (n = 1) Melanoma (n = 1) Mixed (prostate, bladder, lung) (n = 1) Unknown (probably lung) (n = 1)	TMZ, WBRT	WBRT 30 Gy, TMZ 95 mg/m^2 per day, days 1-14	NA	0	3	3	0.176	10	4	PFS: 2.4 mo OS: 4.1 mo
10	SCLC (n = 4) NSCLC (n = 10) Breast (n = 7) Rectal (n = 5) Melanoma (n = 5) Oral cavity (n = 1) Unknown (n = 1)	TMZ, WBRT	WBRT 36Gy, TMZ 60 mg/m^2 per day, days 1-16; subsequent TMZ 200 mg/m^2 per day, days 1-5/28-d cycle	NA	8 (3[2]/2[4] /1[3]/2[5])	11 (5[2]/2[6]/1[3] /1[5]/1[7]/1[8])	19	0.545	2 (1[5]/1[6])	12 (3[2]/1[4] /2[6]/5[3] /1[5])	PFS: 11 mo OS: 12 mo
11	Melanoma	TMZ, WBRT	WBRT 20 or 30 Gy, TMZ 200 mg/m^2 per day, days 1-5/28-d cycle	NA	1[9]	2[9]	3[9]	0.088[9]	9[9]	17[9]	OS: 8 mo mixed response[10]: 5
12	NSCLC (n = 16) SCLC (n = 5) Breast (n = 2) Unknown (n = 2)	TMZ, WBRT	WBRT 40 Gy 5 d/wk, TMZ 75 mg/m^2 per day, days 1-28; subsequent TMZ 200 mg/m^2 per day, days 1-5/28-d cycle	NA	9	14	23	0.959	1	0	OS: 8.6 mo
13	Melanoma	TMZ, WBRT, Thalidomide	WBRT 30 Gy, days 1-5/8-12; TMZ 75 mg/m^2 per day, Weeks 1-6; thalidomide 100 mg/d, Weeks 1-4, 100-400 mg/d Weeks 5, 7, 9	NA	1	2	3	0.077	7	29	TTP: 7 wk OS: 4 mo
14	NSCLC	TMZ, WBRT, Cisplatin	WBRT, TMZ 200 mg/m^2 per day, days 1-5/28-d cycle, cisplatin 75 mg/m^2, day 1/28-d cycle	NA	1[2]/0[3]/0[4]	5[2]/6[3]/8[4]	6[2]/6[3]/8[4]	0.128[2] /0.181[3] /0.17[4]	21[2]/16[3] /10[4]	20[2]/11[3] /29[4]	TTP: 2.3 mo OS: 5 mo
15	NSCLC (n = 17) SCLC (n = 3) Breast (n = 11) Colon (n = 2) Renal (n = 2) Endometrial (n = 1) Bladder (n = 1) Head and neck (n = 1)	TMZ, Vinorelbine	TMZ 150 mg/m^2 per day, days 1-7, 15-21/28-d cycle; vinorelbine 25 or 30 mg/m^2 per day, days 1, 8/28-d cycle	2	1 (NSCLC)	1 (breast)	2	0.055	5	29	PFS: 1.9 mo OS: 5 mo
16	Melanoma	TMZ, Lomustine	TMZ 150 mg/m^2 per day, days 1-5/28-d cycle; lomustine 60 mg/m^2 per day, day 5/56-d cycle	NA	0[9]	0[9]	0[9]	0[9]	1[9]	13[9]	OS: 2 mo
17	Breast (n = 8) NSCLC (n = 6) Colo-rectal (n = 3) Melanoma (n = 1) Ovarian (n = 1)	TMZ, Doxorubicin	TMZ 200 mg/m^2 per day, days 1-5/28-d cycle; pegylated liposomal doxorubicin 35 mg/m^2 per day, day 1/28-d cycle	NA	3	4	7	0.368	8	4	PFS: 5.5 mo OS: 10.0 mo
18	Melanoma	TMZ, arsenic trioxide (ATO)	ATO 0.25 mg/kg per day, days 1-5 in week 0 + 0.35 mg/kg twice weekly/8-wk cycle; TMZ 200 mg/m^2 per day, days 1-5 in weeks 1, 5/8-wk cycle	NA	0	0	0	0	0	5	NA
19	Breast (n = 15) NSCLC (n = 11) SCLC (n = 1) Gastric (n = 1) Melanoma (n = 3) Unknown (n = 1)	TMZ, Cisplatin	TMZ 150-200 mg/m^2 per day, days 1-5/28-d cycle; cisplatin 75 mg/m^2 per day, day 1/28-d cycle	3	1[9] (NSCLC)	1/8[9]	9[9]	0.428	5[9]	6[9]	TTP: 2.9 mo OS: 5.5 mo

20	Melanoma	TMZ, Thalidomide	TMZ 75 mg/m^2 per day, days 1-42/8-wk cycle; thalidomide 200-400 or 100-250 mg/d, days 1-42/8-wk cycle	1	2/0[11]	1/0[11]	3/0[11]	0.214 /0[11]	7/5[11]	4/10[11]	OS: 6 mo
21	Melanoma	A: TMZ, Docetaxel B: TMZ C: TMZ, Cisplatin	A: TMZ 150 mg/m^2 per day, days 1-5/28-d cycle, docetaxel 80 mg/m^2 per day, day 1/28-d cycle; B: TMZ200 mg/m^2 per day, days 1-5/28-d cycle; C: TMZ 200 mg/m^2 per day, days 1-5/28-d cycle, CDDP 75 mg/m^2 per day, day 1/28-d cycle	NA	0/2[11]	6/5[11]	6/7[11]	0.25/ 0.291[11]	5	13	TTP: 2 mo OS: 4.7 mo

[1]Median: Data here are median values; Drugs: Chemotherapy and/or radiotherapy; [2]NSCLC; [3]Breast cancer; [4]SCLC; [5]Melanoma; [6]Rectal cancer; [7]Unknown; [8]Oral cavity cancer; [9]Global response; [10]Mixed response: PR or SD in the brain and PD at other locations; [11]Extracerebral response. TMZ: Temozolomide; NA: Not available; NSCLC: Non-small cell lung cancer; SD: Stable disease; PR: Partial response; CR: Complete response; OR: Objective response; ORR: Objective response rate; PD: Progressive disease; PFS: Progression-free survival; TTP: Time to progression; OS: Overall survival.

agents as treatment for brain metastases. Studies combining temozolomide with whole-brain radiotherapy reported more favourable response rates ranging from 0.176 to 0.959 with median overall survival ranging from 4.1 to 12 mo. In these trials, temozolomide might be shown to possess a radiosensitizing effect[37,38]. In a large review of 1292 patients to define the prognostic factors in patients with brain metastases, Lagerwaard *et al*[39] concluded that the three strongest prognostic factors were performance status, response to steroids, and evidence of systemic disease[40]. In the trial conducted by Addeo *et al*[22], a promising objective response rate of 0.48 (13 of 27 patients) was observed. A possible explanation would be that in this study, 11 of 27 patients were included in first RPA class according to RTOG classification. An objective response rate of 0.82 and two (8%) cases of stable disease were obtained in this group. In contrast, among the 6 patients (22%) included in the third RPA class, no objective response was observed. Besides, the proportion of metastases of lung origin was significantly higher in several studies which got favourable outcomes. Selection bias could have occurred in these trials.

Studies that combined temozolomide with other drugs had also been reported to yield high response rates in patients with brain metastases. The difference between monotherapy and combination therapy could be attributed to the efficacy of other agents. For example, pegylated liposomal doxorubicin had the ability to accumulate in both brain tissue and tumour tissue within the brain[41,42]. Cisplatin, an active cytotoxic drug in solid tumours, might enhance the anti-tumour activity of temozolomide by reducing the activity of the DNA repair enzyme. However, most of patients involved in the studies were heavily pre-treated and failed prior therapy. Perhaps, the chemotherapeutic sensitization of temozolomide could be attributed to the improvement of the therapeutic effect in combination therapy. In addition, the dosage of other chemotherapeutic agents might be reduced to alleviate toxic reaction and improve patients' quality of life. The trial of temozolomide plus pegylated liposomal doxorubicin indicated that this chemotherapy regiment was well tolerated in elderly patients. This implied that temozolomide/pegylated liposomal doxorubicin could be an effective therapeutic strategy for patients who were not suitable for conventional treatments because of the presence of brain metastases or old age.

In conclusion, since the studies in which temozolomide was used as a single agent usually achieved minimal outcomes, monotherapy might not be an optimal therapeutic strategy. However, the combination of temozolomide with whole-brain radiotherapy or other agents showed the potential to improve clinical outcomes of patients with brain metastases. It is worth re-examining the effects of temozolomide combined with other drugs or whole-brain radiotherapy on survival of patients with brain metastases from solid tumours in a randomized phase Ⅲ study.

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