Efficacy and side effects of dacarbazine in comparison with temozolomide in the treatment of malignant melanoma: a meta-analysis consisting of 1314 patients

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The widespread prevalence of melanoma, one of the most malignant forms of skin cancer, is increasing rapidly. Two chemotherapeutic regimens are commonly used for the palliative treatment of malignant melanoma: intravenous administration of single-agent dacarbazine or oral administration of temozolomide. The aim of this study was to compare the effectiveness and side effects of dacarbazine with those of temozolomide through a meta-analysis. A thorough literature bibliography search was conducted up to 2012 to gather and review all randomized clinical trials comparing the use of dacarbazine with that of temozolomide in the treatment of malignant melanoma. Three head-to-head randomized clinical trials comprising 1314 patients met the criteria and were included. Comparison of temozolomide with dacarbazine yielded a nonsignificant relative risk (RR) of 0.83 [95% confidence interval (CI)=0.26–2.64, *P*=0.76] for complete response, a nonsignificant RR of 1.05 (95% CI=0.85–1.3, *P*=0.65) for stable disease, and a nonsignificant RR of 2.64 (95% CI=0.97–1.36, *P*=0.11) for disease control rate. The RR for nonhematologic side effects and hematologic side effects, such as anemia, neutropenia, and thrombocytopenia, of temozolomide compared with dacarbazine in patients with malignant melanoma was nonsignificant in all cases, but the RR for lymphopenia of temozolomide compared with dacarbazine was 3.79 (95% CI=1.38–10.39, *P*=0.01), which was significant. Although it is easier to administer oral medication, according to the results, there is no significant difference in the efficacy and side effects of these two drugs. Owing to the higher cost of treatment with temozolomide and the increased prevalence of lymphopenia on using temozolomide, use of dacarbazine as the first choice treatment for malignant melanoma is suggested. *Melanoma Res* 23:381–389 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

The most aggressive and deadly form of skin cancer is melanoma [1]. Melanoma is the fifth most common type of cancer among men, and the sixth among women [2]. The worldwide incidence of malignant melanoma is increasing, especially among fair-skinned people, by 3–7% per annum [3,4]. It is likely for melanomas to metastasize to any internal organ, especially the brain. The goal of treatment is to manage metastatic melanoma patients, as the condition is generally incurable. To decrease mortality, early diagnosis is very important [2]. Patients with advanced metastatic melanoma have few available treatment options. One of the standard approaches in the palliative management of patients with metastatic melanoma is the intravenous administration of single-agent dacarbazine [5]. Dacarbazine is a cell-cycle nonspecific antineoplastic agent, which functions as an alkylating agent that binds to specific sections of DNA and prevents cell division, resulting in cell death. It requires metabolic activation in the liver to convert to its active metabolite, 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC) [6]. Thereafter, this metabolite decomposes into a purine, which undergoes nucleic acid biosynthesis, and a methyldiazonium ion, which is the active alkylating species [7]. In contrast, temozolomide is an orally bioavailable alkylating agent that is useful as an alternative to dacarbazine. It is rapidly and completely absorbed after oral administration and, unlike dacarbazine, does not require the CYP450 system for metabolic transformation and conversion into the active metabolite (MTIC); it undergoes spontaneous chemical degradation at physiological pH to form MTIC [7,8].

Antitumor activities of some new drugs and combinations of chemotherapeutic agents have been evaluated in the recent years, although a significant difference from standard care regimens has not been indicated [9].

The potential value of oral compared with intravenous chemotherapy is obvious; however, the oral agent has a higher cost. If the efficacy and adverse effects of these two drugs are equivalent, these financial and patient preference trade-offs should be confronted. Some studies have compared them in clinical trials, but no meta-analyses have yet been conducted. The aim of this study was to compare the efficacy and side effects

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of dacarbazine with those of temozolomide in the treatment of malignant melanoma through a meta-analysis.

Methods

Data sources

To compare the efficacy of these two drugs, a systematic review and meta-analysis were conducted. All published articles comparing use of dacarbazine and temozolomide in the treatment of malignant melanoma were reviewed. For this purpose, PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched. The search terms were 'dacarbazine' and 'temozolomide' and 'malignant melanoma'. Data were collected from 1965 to March 2012.

Study selection

Controlled trials comparing the efficacy of dacarbazine with that of temozolomide in patients with malignant melanoma were considered. 'Response to treatment' included 'complete response', 'partial response', 'stable disease', and the side effects were the key outcomes of interest. Published studies and trials were disqualified if the two comparative arms for using other drugs were not similar or their outcomes did not show any relationship with efficacy. Thereafter, data on patient characteristics, therapeutic regimens, dosage, trial duration, and outcome measures were extracted from the selected studies. The methodological quality of included trials was assessed using the Jadad score, which assesses descriptions of randomization, blinding, and dropouts (withdrawals) in trials [10].

Assessment of trial quality

According to the Jadad score, the quality of the studies is determined on the basis of their descriptions of randomization, blinding, and dropouts (withdrawals) [10]. The quality scores range from 0 to 5, among which low quality is defined by a score of 2 or less and high quality is defined by a score of at least 3.

Statistical analysis

Data from selected studies were extracted in the form of 2×2 tables according to study characteristics. The included studies were weighted by effect size and pooled. Data were analyzed using StatsDirect 2.7.9 software. Relative risks (RR) and 95% confidence intervals (95% CIs) were calculated using the Der Simonian–Laird (for random effects) method. The Cochrane Q-test was used to test heterogeneity, and P-value less than 0.05 was considered significant. In the case of heterogeneity or where very few studies were included in the analysis, the random-effects model was used. The event rate in the experimental (intervention) group was compared with the event rate in the control group using the L'Abbe plot as an aid to explore the heterogeneity in effect estimates.

Results

The electronic searches yielded 547 items: 77 from PubMed, 11 from Cochrane Central, 174 from Web of Science, and 285 from Scopus. Among these, the full text of five trials was scrutinized. Two reports were considered ineligible. On the basis of the inclusion criteria, only three head-to-head trials including 1314 patients with malignant melanoma were meta-analyzed. Approximately half of the patients were allocated to the temozolomide arm and half to the dacarbazine arm (Fig. 1). As regards trial quality, two trials had a quality score of 2 and one trial had a quality score of 3 (Table 1). Characteristics of patients, regimens, and duration of treatment in each study are reported in Table 1.

Efficacy

Effect of temozolomide in comparison with dacarbazine in the treatment of patients with advanced metastatic malignant melanoma

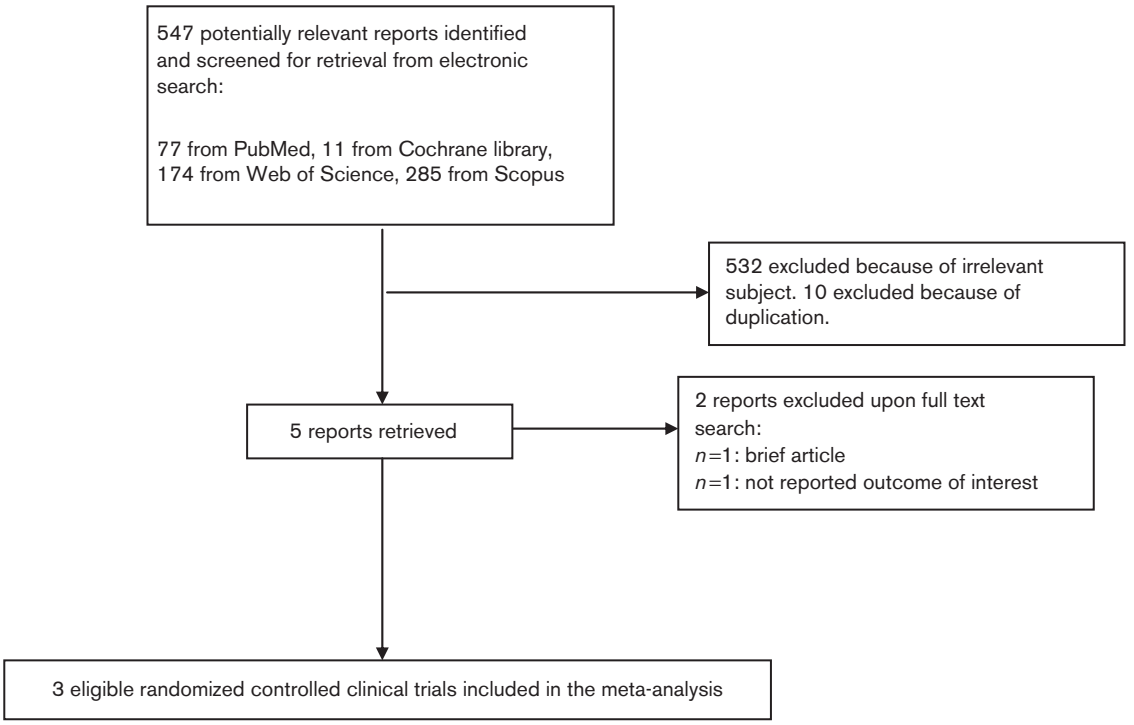
Complete response: The summary of RR for complete response of temozolomide in comparison with dacarbazine in patients with advanced metastatic malignant melanoma for three included trials [11–13] was 0.83 (95% CI = 0.26–2.64), which was nonsignificant ($P = 0.76$; Fig. 2a). The Cochrane Q-test for heterogeneity indicated that the studies were not heterogeneous ($P = 0.11$; Fig. 2b) and could be combined; however, because of the very small number of studies included, the random-effects model for individual RR and the summary of RR was applied.

Partial response: The summary of RR for partial response of temozolomide in comparison with dacarbazine in patients with advanced metastatic malignant melanoma for two included trials [11,13] was 1.35 (95% CI = 0.95–1.91), which was nonsignificant ($P = 0.1$; Fig. 3a). The Cochrane Q-test for heterogeneity indicated that the studies were not heterogeneous ($P = 0.61$; Fig. 3b) and could be combined; however, because of the very small number of studies included, the random-effects model for individual RR and the summary of RR was applied.

Stable disease: The summary of RR for 'stable disease' of temozolomide in comparison with dacarbazine in patients with advanced metastatic malignant melanoma for three included trials [11–13] was 1.05 (95% CI = 0.85–1.3), which was nonsignificant ($P = 0.65$; Fig. 4a). The Cochrane Q-test for heterogeneity indicated that the studies were not heterogeneous ($P = 0.92$; Fig. 4b) and could be combined; however, because of the very small number of studies included, the random-effects model for individual RR and the summary of RR was applied (Table 2).

Disease control rate: The summary of RR for disease control rate of temozolomide in comparison with dacarbazine in patients with advanced metastatic malignant melanoma for two included trials [11,13] was 2.64 (95% CI = 0.97–1.36), which was nonsignificant ($P = 0.11$). The Cochrane Q-test for heterogeneity indicated that the

Fig. 1



Flow diagram for study selection.

Table 1 Characteristics of three selected randomized control trials

References	Duration	Patient population	Treatment	Jadad score
Middleton *et al.* [11]	2 years	305 patients with MM 156 patients on TMZ 149 patients on DTIC	TMZ: orally q.d. for 5 days, starting dose of 200 mg/m^2 every 28 days DTIC: IV q.d. for 5 days, starting dose of 250 mg/m^2 every 21 days	2
Chiarion-sileni *et al.* [12]	4 years	150 patients with MM 75 patients on CTI 75 patients on CDI	CTI: cisplatin IV 75 mg/m^2 on day 1 Oral TMZ of 200 mg/m^2/day for 5 days, IL-2 3 000 000 IU SC b.i.d. on days 9–17, G-CSF 300 μg q.d. SC on days 6–12, every 28 days CDI: cisplatin IV 75 mg/m^2 on day 1 IV DTIC 800 mg/m^2 on day 1, IL-2 3 000 000 IU SC b.i.d. on days 9–17, G-CSF 300 μg q.d. SC on days 6–12, every 28 days	3
Patel *et al.* [13]	3 years	859 patients with MM 429 patients on TMZ 430 patients on DTIC	TMZ: orally q.d. 150 mg/m^2/day for 7 days, every 2 weeks DTIC: IV 1000 mg/m^2/day on day 1, every 3 weeks	2

b.i.d., twice a day; CDI, DTIC-based chemotherapy; CTI, TMZ-based chemotherapy; DTIC, dacarbazine; IV, intravenous; MM, malignant melanoma; q.d., once a day; SC, subcutaneous; TMZ, temozolomide.

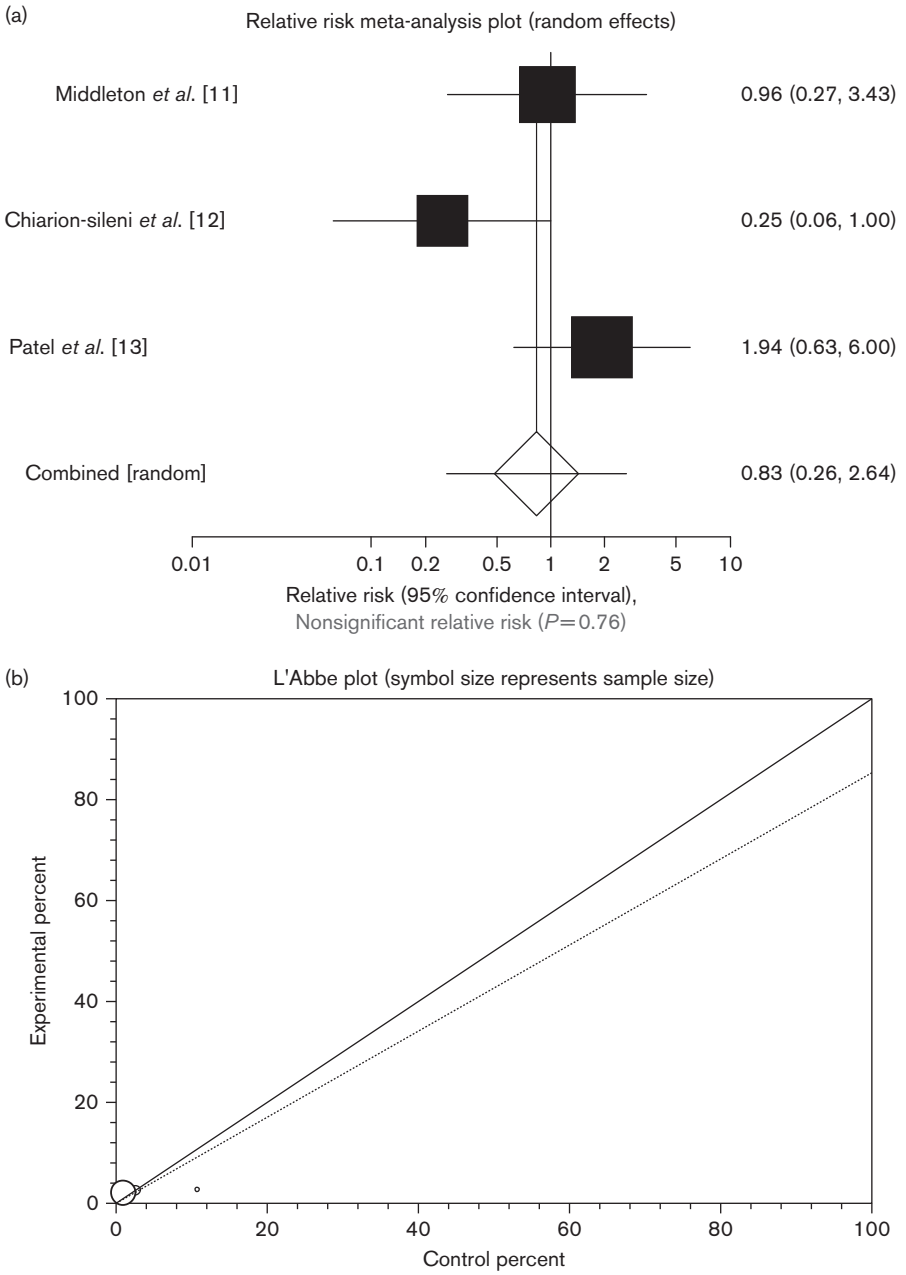
studies were not heterogeneous ($P = 0.85$) and could be combined; however, because of the very small number of studies included, the random-effects model for individual RR and the summary of RR was applied (Table 2).

Side effects

Nonhematologic side effects of temozolomide in comparison with dacarbazine in the treatment of patients with advanced metastatic malignant melanoma

The summary of RR for fatigue, fever, anorexia, and constipation of temozolomide in comparison with dacarbazine in patients with advanced metastatic malignant melanoma for two included trials [11,12] was 0.99 (95% CI = 0.79–1.25), 0.84 (95% CI = 0.48–1.47), 0.88 (95% CI = 0.58–1.33), and 1.04 (95% CI = 0.75–1.45), respectively, all of which were nonsignificant. The Cochrane *Q*-test for heterogeneity indicated that none of the studies on outcomes were heterogeneous and that all studies could be combined; however, because of the very small number of studies included, the random-effects model for individual RR and the summary of RR was applied (Table 3).

Fig. 2

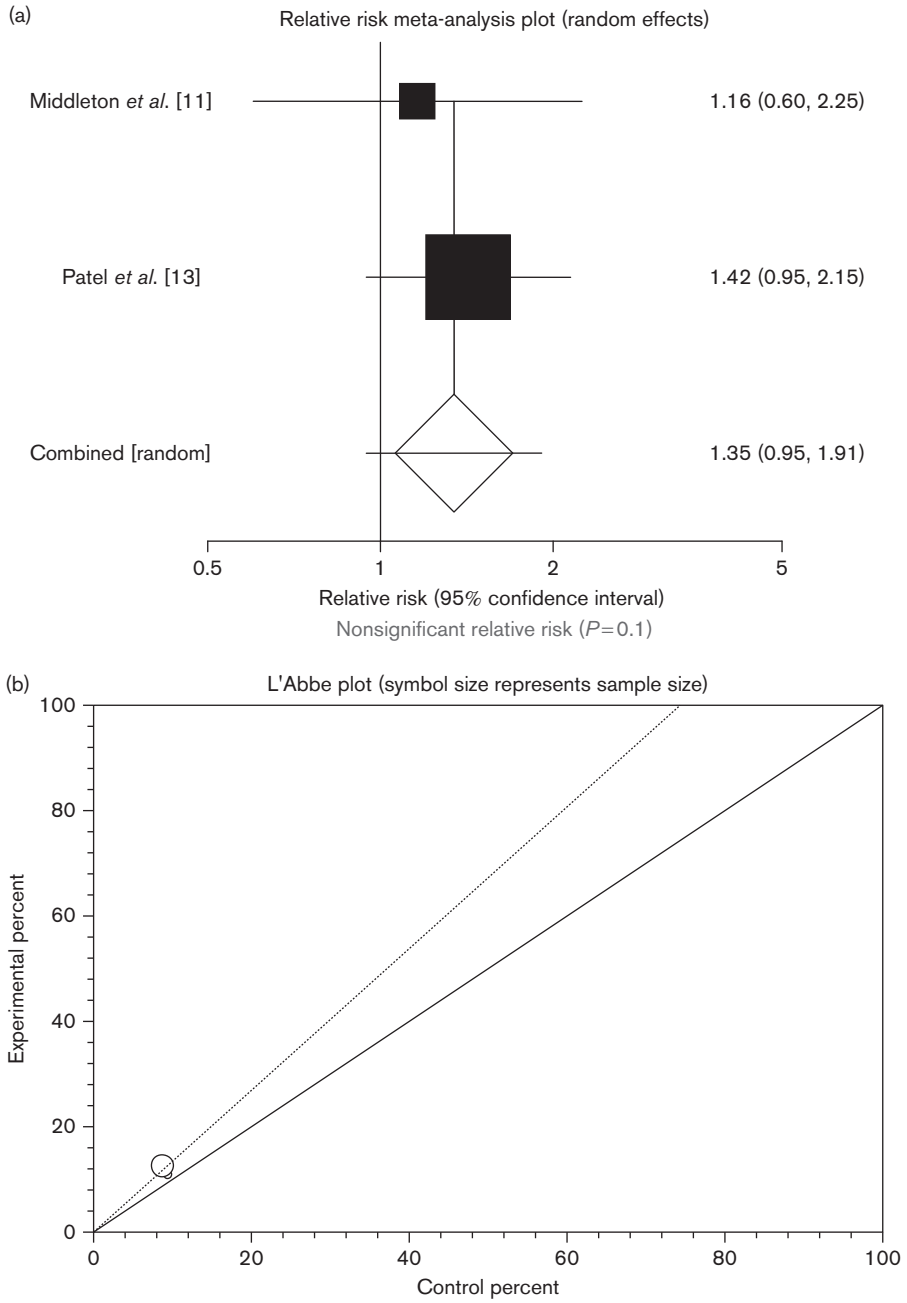


(a) Individual and pooled relative risks for the outcome of 'complete response' in the studies considering temozolomide compared with dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. (b) Heterogeneity indicators for the outcome of 'complete response' in the studies considering temozolomide compared with dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. No heterogeneity ($P=0.11$).

Hematologic side effects of temozolomide in comparison with dacarbazine in the treatment of patients with advanced metastatic malignant melanoma

The summary of RR for anemia, neutropenia, and thrombocytopenia (for all grades) of temozolomide in comparison with dacarbazine in patients with advanced metastatic malignant melanoma for two included trials [11,12] was 1.14 (95% CI = 0.57–2.27), 1.09 (95% CI = 0.74–1.60), and 0.97 (95% CI = 0.65–1.46), respectively, all of which were nonsignificant. The Cochrane *Q*-test for heterogeneity indicated that none of the studies on outcomes were heterogeneous and that all studies could be combined; however, because of very small number of studies included, the random-effects model for individual RR and the summary of RR was applied (Table 4).

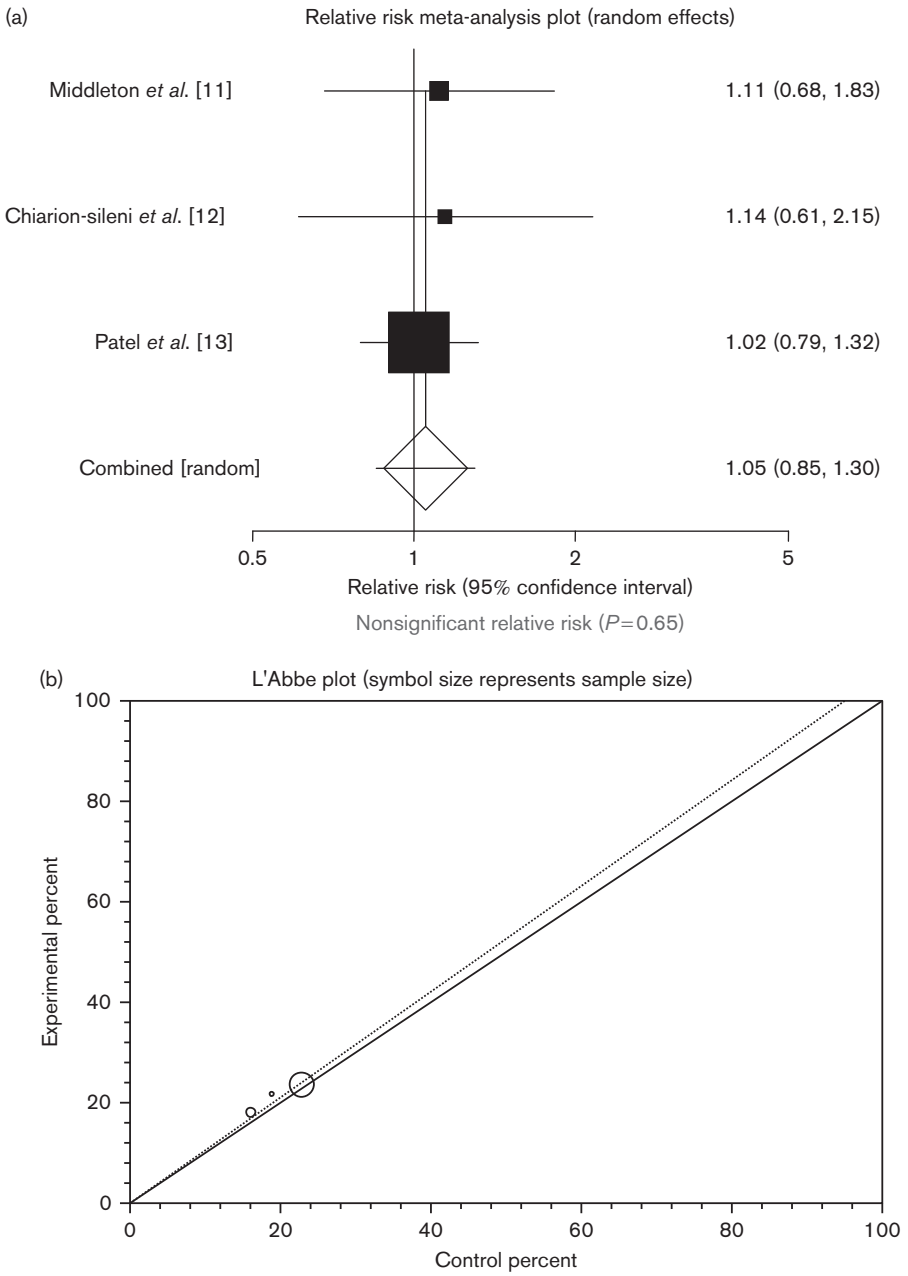
Fig. 3



(a) Individual and pooled relative risks for the outcome of 'partial response' in the studies considering temozolomide compared with dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. (b) Heterogeneity indicators for the outcome of 'partial response' in the studies considering temozolomide compared with dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. No heterogeneity ($P=0.61$).

The summary of RR for anemia, neutropenia, and thrombocytopenia (for grades 3 and 4) of temozolomide in comparison with dacarbazine in patients with advanced metastatic malignant melanoma for three included trials [11–13] was 1.8 (95% CI = 0.9–3.62), 0.97 (95% CI = 0.48–1.97), and 1.44 (95% CI = 0.9–2.3), respectively, all of which were nonsignificant. The Cochrane *Q*-test for heterogeneity indicated that none of the studies on outcomes were heterogeneous and that all studies could be combined; however, because of the very small number of studies included, the random-effects model for individual RR and the summary of RR was applied. The summary of RR for lymphopenia (for grades 3 and 4) of temozolomide in comparison with dacarbazine

Fig. 4



(a) Individual and pooled relative risks for the outcome of 'stable disease' in the studies considering temozolomide compared with dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. (b) Heterogeneity indicators for the outcome of 'stable disease' in the studies considering temozolomide compared with dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. No heterogeneity ($P=0.92$).

in patients with advanced metastatic malignant melanoma for two included trials [12,13] was 3.79 (95% CI = 1.38–10.39), which was significant ($P = 0.01$). The Cochrane Q-test for heterogeneity indicated that the studies were not heterogeneous and could be combined; however because of the very small number of studies included, the random-effects model for individual RR and the summary of RR was applied (Table 4).

Discussion

After using single-agent dacarbazine intravenously in the treatment of malignant melanoma for several years, the oral agent temozolomide was developed, which is more convenient for use by patients. Middleton *et al.* [11], for the first time in the literature, compared temozolomide and dacarbazine and showed that their efficacies in the treatment of melanoma were the same. In 2011, in

Table 2 Response to treatment

	References					
	Middleton *et al.* [11]		Chiarion-sileni *et al.* [12]		Patel *et al.* [13]	
Results	TMZ ($n=156$) [n (%)]	DTIC ($n=149$) [n (%)]	CTI ($n=74$)	CDI ($n=74$)	TMZ ($n=401$) [n (%)]	DTIC ($n=388$) [n (%)]
Complete response	4 (2.6)	4 (2.7)	2	8	8 (2)	4 (1)
Partial response	17 (10.9)	14 (9.4)	ND	ND	50 (12.5)	34 (8.8)
Stable disease	28 (17.9)	24 (15.8)	16	14	94 (23.4)	89 (22.9)
Disease control rate	49 (31.4)	42 (27.9)	ND	ND	152 (37.9)	127 (32.7)
Progressive disease	95 (60.9)	94 (63.1)	ND	ND	230 (57.4)	246 (63.4)
Not treated/ineligible	12 (7.7)	13 (8.7)	ND	ND	19 (4.7)	15 (3.9)
Complete/partial response	21 (13.5)	18 (12.1)	ND	ND	ND	ND

CDI, DTIC-based chemotherapy; CTI, TMZ-based chemotherapy; DTIC, dacarbazine; ND, not determined; TMZ, temozolomide.

Table 3 Toxicity and nonhematologic adverse events

	References									
	Middleton *et al.* [11]				Chiarion-sileni *et al.* [12]				Patel *et al.* [13]	
	TMZ ($n=151$)		DTIC ($n=142$)		CTI ($n=74$)		CDI ($n=74$)		TMZ ($n=420$)	DTIC ($n=419$)
Adverse events	All grades	Grades (3–4)	All grades	Grades (3–4)	All grades	Grades (3–4)	All grades	Grades (3–4)	Grades (3–4)	Grades (3–4)
Asthenia	18	4	20	1	ND	ND	ND	ND	ND	ND
Fatigue	30	4	25	3	43	13	45	12	25	21
Fever	16	3	25	3	40	7	38	5	ND	ND
Headache	33	9	17	1	ND	ND	ND	ND	ND	ND
Pain	51	10	55	18	ND	ND	ND	ND	ND	ND
Anorexia	22	0	28	3	17	4	15	6	8	<4
Constipation	45	4	41	4	9	0	8	0	8	<4
Nausea	78	6	54	5	ND	ND	ND	ND	12	12
Vomiting	51	7	34	5	ND	ND	ND	ND	17	8
Somnolence	18	0	18	1	ND	ND	ND	ND	ND	ND
Diarrhea	ND	ND	ND	ND	5	0	5	0	ND	ND
Liver function	ND	ND	ND	ND	18	5	23	3	ND	ND
Nausea/vomiting	ND	ND	ND	ND	44	7	47	11	ND	ND
Dyspnea	ND	ND	ND	ND	ND	ND	ND	ND	8	8
Dizziness	ND	ND	ND	ND	ND	ND	ND	ND	4	<4
Neurological	ND	ND	ND	ND	ND	ND	ND	ND	4	4
Cardiac	ND	ND	ND	ND	ND	ND	ND	ND	<4	4
Other problems	ND	ND	ND	ND	ND	ND	ND	ND	4	8

CDI, DTIC-based chemotherapy; CTI, TMZ-based chemotherapy; DTIC, dacarbazine; ND, not determined; TMZ, temozolomide.

Table 4 Toxicity and hematologic adverse events

	References									
	Middleton *et al.* [11]				Chiarion-sileni *et al.* [12]				Patel *et al.* [13]	
	TMZ ($n=151$)		DTIC ($n=142$)		CTI ($n=74$)		CDI ($n=74$)		TMZ ($n=417$)	DTIC ($n=416$)
Adverse events	All grades	Grades (3–4)	All grades	Grades (3–4)	All grades	Grades (3–4)	All grades	Grades (3–4)	Grades (3–4)	Grades (3–4)
Anemia	12	3	15	1	35	7	23	3	12	8
Neutropenia	7	4	4	3	29	17	28	11	41	66
Thrombocytopenia	14	10	13	11	22	7	23	5	46	25
Leukocytes	ND	ND	ND	ND	21	5	14	2	ND	ND
Lymphopenia	ND	ND	ND	ND	10	3	7	2	187	37
Leukopenia	ND	ND	ND	ND	ND	ND	ND	ND	37	33

CDI, DTIC-based chemotherapy; CTI, TMZ-based chemotherapy; DTIC, dacarbazine; ND, not determined; TMZ, temozolomide.

a study, the researchers extended the dose of temozolomide to determine whether the extended schedule of temozolomide is more effective than standard single-agent dacarbazine. They believed that sequential dosing of temozolomide could overcome resistance and increase the efficacy and toxicity of temozolomide. Thereafter, they concluded that an extended dose of temozolomide is applicable and safe but does not improve the median overall survival and progression-free survival in metastatic melanoma patients compared with the standard dose of

dacarbazine [13]. This is the first time that a meta-analysis has been carried out to compare the efficacies and adverse effects of these two drugs; however, we had only three randomized controlled trials with similar regimens in two arms that compared dacarbazine and temozolomide. Of the five articles with relevant subjects, we had to exclude two articles: one of which was a brief article [14] and, in the other, the results of treatment with the two drugs had not been separated [15]. As all trials were imperfect, they could not be used in the meta-analysis as they might cause bias. To use trials, we need to assess their qualities. One of the ways to assess trial quality is to use a validated tool. The methodological quality of included trials was assessed using the Jadad score. Jadad scoring is a valid and easy tool to assess clinical trial quality. This scale includes three items that are presented as questions, to which the answers can be 'yes' or 'no', and judges descriptions of randomization, blinding, and dropouts (withdrawals) in trials. This scale yields scores ranging from 0 to 5. If the study was described as randomized or double-blind, 1 point was awarded in each case, and if there was a description of withdrawals, an additional point was awarded. If the methods of randomization/blinding were appropriate, 1 additional point each was awarded, and in the case of inappropriateness, the relevant item was given 0 points. If a trial was awarded 2 points or less, it could be judged as being of poor quality [10].

In this case, because of the different forms of dosage of temozolomide (oral) and dacarbazine (parenteral), the trials already lost 2 points of blinding and thus got 3 or 2 points. The results of this meta-analysis indicate that incidence of adverse effects with temozolomide does not differ with that of dacarbazine. In two trials [12–13], lymphopenia was more common in the temozolomide group. In addition, on the basis of the nonsignificant difference in 'response to treatment' we conclude that the oral agent is not more effective. The selection of a drug for treatment depends on its efficacy, safety, and price. One of the objectives of the National Drug Policy (NDP) in Iran is to provide all patients with equal access to essential drugs [16–18]. To implement this idea, medicines should be made affordable and balanced utilization of medicines should be ensured by healthcare providers [19]. Economic evaluation of medicines is a tool to assess NDP criteria such as accessibility and equity [17,20]. Considering health outcomes, the nonsignificant difference in efficacy between these two drugs, the lower costs of treatment with dacarbazine (in the USA, temozolomide is still protected by patent and patients do not have access to generic forms of this drug), the equal rate of adverse events compared with temozolomide, and the lower prevalence of lymphopenia, we suggest dacarbazine to be the first choice of treatment for malignant melanoma. In addition, it is not wise to initiate temozolomide therapy when the dacarbazine regimen fails. Among standard agents used in the treatment of malignant melanoma, including dacarbazine, temozolomide is the only agent that penetrates the blood–brain barrier. In patients with brain metastases from melanoma, temozolomide can be used in addition to surgery and radiation if systematic treatment is required [21].

Patients can use temozolomide when dacarbazine is found to be intolerable. The more convenient route of administration of temozolomide makes physicians initiate treatment with the temozolomide regimen.

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Conflicts of interest

There are no conflicts of interest.

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