Cancer Chemother Pharmacol (2008) 62:293–298
DOI 10.1007/s00280-007-0606-5

ORIGINAL ARTICLE

Temozolomide in combination with fotemustine in patients with metastatic melanoma

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Received: 24 April 2007 / Accepted: 14 September 2007 / Published online: 2 October 2007

Abstract
Purpose Temozolomide and fotemustine are both active drugs for treating metastatic melanoma. The present study was designed to assess the efficacy and safety of combination therapy with temozolomide + fotemustine in patients with metastatic melanoma.
Methods Forty patients (median age 50.5 and 22 males) with pathologically confirmed, unresectable, AJCO stage IV melanoma were enrolled into the study. The primary endpoints were tumor response and safety. Patients received oral temozolomide 125 mg/m^2 on days 1–7 and intravenous fotemustine 80 mg/m^2 on day 3 every 3 weeks.
Results Fourteen (35%) patients achieved an objective response, including 3 (7.5%) complete and 11 (27.5%) partial responses. Median overall survival time was 6.7 months and 6-month survival rate was 57.4%. Myelosupression, particularly thrombocytopenia, was the primary toxicity.
Conclusion The regimen, temozolomide combined with fotemustine, is an active and moderately safe first-line chemotherapy regimen with acceptable and easily manageable toxicities in patients with metastatic melanoma.

Keywords Melanoma · Metastatic · Temozolomide · Fotemustine

Introduction

The prognosis remains poor for melanoma patients with systemic metastases; median survival is only 6 months [1–3]. Unfortunately, this pessimistic and disappointing reality has not been changed in the past few years. Therefore, novel chemotherapy agents or combinations are needed in the treatment of advanced melanoma. Systemic therapy with palliative intent is the mainstay of the treatment.

Presently, dacarbazine (DTIC) has become the standard chemotherapy for metastatic melanoma, with a response rate of approximately 20%, and complete response (CR) occurs in less than 5% of treated patients [2, 3]. Response duration is only a few months. No other agents have a better response rate than dacarbazine. Taken together, to date, phase III trials have shown no compelling evidence to support the value of combination chemotherapy in patients with metastatic melanoma [3–5].

Temozolomide, a novel oral alkylating agent, has a high oral bioavailability and extensive tissue distribution, including penetration through the blood-brain barrier [6]. In addition to these advantages of temozolomide over dacarbazine, patients with metastatic melanoma achieved overall response rates of nearly 20% with single-agent temozolomide as similar as DTIC [7–9]. This has been an expected finding because of both of them are metabolized to the same active alklylating agent, which would explain their similar activity in melanoma. In a large randomized phase III trial, it demonstrated equivalent response rates, overall survival, and toxicity of single-agent DTIC [9]. Moreover, temozolomide treatment was associated with improvement in progression-free survival, and quality of life compared with DTIC. After this study, a more convenient, possibly at least an equally effective therapy to dacarbazine is now available for treatment of patients with advanced melanoma.

Similar to DTIC, in order to enhance the efficacy of single-dose temozolomide treatment, various temozolomide-containing combination protocols were studied in patients

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with metastatic melanoma [10–13]. Additionally, in many investigations, temozolomide has demonstrated markedly schedule-dependent anticancer activity [14, 15]. One mechanism that has been proposed to explain the schedule-dependent anticancer activity of temozolomide, especially on protracted schedules may lead to marked, cumulative, and sustained inactivation of O^6-alkyl-guanine-DNA alkyltransferase (AGAT), an ubiquitous DNA repair enzyme. As a consequence of this function, AGAT confers cellular resistance to cytotoxic agents that principally target the O^6 position of guanine, including nitrosoureas [15]. Tumors with high AGAT expression like melanoma have demonstrated marked resistance to nitrosoureas agents, including fotemustine. Therefore, administering temozolomide with protracted and low-dose schedules that result in cumulative and sustained inactivation of AGAT may both autoenhance cytotoxic activity of their own and other combined drugs that principally target the O^6 position of guanine by reducing the cell capacity for DNA repair and intrinsic drug resistance [15].

The nitrosourea analogs, especially fotemustine, have shown modest activity in patients with metastatic melanoma [2, 3]. Fotemustine has been more extensively studied, with response rates averaging 20%, responses were partial, and the median response duration was only several months. As an older and one of the most effective drugs against melanoma, fotemustine has been a reasonable choice in combination with temozolomide in treating metastatic melanoma. The rationale for evaluating this regimen was, in part, the single-agent activity of both agents against melanoma; furthermore, temozolomide had been shown to reduce AGAT activity in vitro, suggesting that temozolomide might enhance the antitumor activity of fotemustine by reducing AGAT activity [16, 17].

Despite these available positive findings in this area, unfortunately, there is no clinical study to investigate the efficacy of combination therapy with temozolomide + fotemustine in patients with advanced melanoma in literature. The present study was designed to assess the efficacy and safety of combination therapy with temozolomide + fotemustine in patients with metastatic melanoma.

Patients and methods

Patients

Eligible adult patients with histologically confirmed metastatic (stage IV) melanoma were required to have measurable or assessable disease, have adequate renal, hepatic and bone marrow functions. The patients were required to have an adequate ECOG performance status (0–2) and life expectancy of at least 3 months. Radiotherapy to nonindicator lesions or adjuvant immunotherapy with interferon-alpha more than 4 weeks earlier was permitted. Patients with asymptomatic brain metastases were also enrolled, provided that they had additional disease sites and did not require immediate whole brain irradiation. Patients who had received previous cytotoxic treatment for metastatic disease were not enrolled. This trial was approved by the local ethical committee and written informed consent was obtained from all patients before study.

Treatment

Temozolomide was administered orally under fasting conditions daily for 7 consecutive days at a single dose of 125 mg/m^2 and fotemustine was given intravenously as a 60-min infusion on day 3, 4 h after temozolomide at a dose of 80 mg/m2. Treatment cycles were repeated on an outpatient basis every 21 days in the absence of disease progression or severe toxicity. Patients were premedicated for providing antiemesis with standard serotonine antagonists and dexamethasone. G-CSF was not used prophylactically, but it was recommended for patients who had previously experienced either febrile neutropenia or grade IV neutropenia lasting more than 5 days after occurrence.

The temozolomide (from 125 mg/m^2 to 100 mg/m^2) and fotemustine (from 80 mg/m^2 to 60 mg/m^2) dosages were reduced by nearly 20–25% of the starting dose when the severe (grade 3 or 4) hematologic toxicity occurred. A 50% dose reduction was required in cases of severe nonhematologic toxicity. Patients requiring more than two dose reductions and for whom dosing was delayed for up to 3 weeks were removed from the study. Drug administration was postponed by 1 week if there was no full hematologic recovery from the prior cycle of treatment. Patients with progressive disease (PD) at any time were withdrawn from the study; patients with stable disease (SD) or who were responsive to therapy, received a maximum of four cycles. Toxicity was evaluated according to the NCI-CTC v3.0 grading system before each cycle of therapy. Patients were assessable for toxicity if they had received at least one cycle of treatment.

Evaluation

A prestudy evaluation was completed within 2 weeks before receiving the study drugs. On entry, all patients had a complete medical history and physical examination. Complete blood cell count with differential and platelet count, and standard biochemical analysis were performed during every treatment cycle. Before each cycle, common toxicity criteria, performance status and measurement of clinically assessable disease were documented.

Patients were evaluated for response if they received one or more cycles of treatment. If there was no disease progression after one cycle, at least two cycles were administered. Tumor response was evaluated by physical examination, chest X-ray, computed tomography scan, or other tests after completion of the second cycle of chemotherapy.

The primary efficacy variable was the proportion of patients who attained a complete or partial response (PR). Objective tumor responses were evaluated according to Response Evaluation Criteria In Solid Tumors criteria. A CR was defined as complete disappearance of all lesions. A PR was defined as $a \geq 30\%$ decrease in the sum of longest diameter of all measured lesions. SD was defined as no significant change in measurable and nonmeasurable disease. PD was defined as $a \geq 20\%$ increase in the product of the two longest perpendicular diameters of any measurable lesions or in the estimated size of nonmeasurable disease, the appearance of a new lesion, or the reappearance of old lesions.

Statistical methods

This study was designed to detect a response rate of at least 20%. A design was used with up to 40 patients with the stopping rule if the response rates was less than 20% regarding 95% CI. The regimen would be considered worthy of further study if eight or more confirmed responses were observed, provided that toxicity was acceptable.

The primary endpoints of the study were to determine the objective response rate and safety of the regimen. Survival parameters were our secondary endpoints. Overall survival time was defined as the time from initiation of treatment to the date of death or final data analysis. Survival rates were estimated by the method of Kaplan–Meier.

Results

Patients characteristics

Forty patients with chemotherapy-naive metastatic melanoma were enrolled into the study. Characteristics of patient and tumor were summarized in Table 1. The median age was 50.5 years (range 30–79), most of the patients were males and in good performance status. The axial localization was the primary tumor site and the majority of metastatic disease was extensive and widespread (M1c). Other various serum parameters concerning disease are shown in Table 1. Nearly half of the patients had been treated with interferon-alpha for adjuvant treatment.

Table 1 Patient characteristics

Parameter	*n* (%)
No. of patients	40
Age, years median (range)	50.5 (31–79)
Gender	
Male	22 (55)
Female	18 (45)
Primary localization	
Head and neck	7 (17.5)
Body	11 (27.5)
Extremity	15 (37.5)
Mucosa	6 (15.0)
Unknown	1 (2.5)
Site of metastasis	
Soft tissue, lymph node, in-transit	11 (27.5)
Lung	3 (7.5)
Viscera	4 (10.0)
Mixted	22 (55.0)
No. of metastatic sites	
Single	11 (27.5)
Multiple	29 (72.5)
Stage (M1)	
M1a + b	12 (30.0)
M1c	28 (70.0)
Performance status (ECOG)	
0	19 (47.5)
1	12 (30.0)
2	9 (22.5)
Serum neuron-specific enolase	
Normal	14 (61)
Elevated	9 (39)
Serum lactate dehydrogenase	
Normal	18 (45)
Elevated	22 (55)
Hemoglobin	
Normal	27 (67.5)
Low	13 (32.5)
Albumin	
Normal	34 (92)
Low	3 (8)
Prior adjuvant interferon treatment	
Yes	17 (57.5)
No	23 (42.5)

Safety

Toxicities observed during 103 cycles of chemotherapy are summarized in Table 2. Hematological toxicity was panmyelocytopenia. Especially, thrombocytopenia and followed

Table 2 Toxicity profile

Toxicity	NCI worst toxicity (number of patients)			
	1	2	3	4
Hematological				
Leucopenia	2	6	6	1
Neutropenia	5	5	4	1
Anemia	15	6	1	2
Thrombopenia	3	3	9	5
Biochemical				
Creatinine	1	1	0	0
Transaminase	1	0	0	0
Bilirubin	0	0	0	0
Nonhematological				
Nausea	17	12	0	
Vomiting	14	10	0	0
Diarrhea	12	0	0	0
Stomatitis	3	4	0	0
Alopecia	2	0		
Pulmonary	0	0	0	0
Infection	0	0	0	0

by neutropenia were the principal dose-limiting toxicities. Severe (grade III/IV) neutropenia was observed in five (12.5%) patients and only one (2.5%) had complicated febrile neutropenia. These patients recovered uneventfully after treatment with antibiotics and G-CSF usage. Grade III and IV anemia was seen in three (7.5%) patients, with four (10.0%) patients receiving a total of 11 units of packed red blood cells. Severe thrombocytopenia was noted in 14 (35%) patients and no patient had less than 10,000/mm^3, therefore, platelet transfusion was not given. There was no clinically significant bleeding complication. No severe toxicity in biochemical parameters was determined.

Patients were managed with various antiemetic agents; dose adjustment was not done due to emesis. No other severe nonhematologic parameter was found and side effects were well tolerated and managed.

Dose delivery

A total of 103 cycles were delivered, with a median of two cycles per patient (range, 1–4). Permanent dose reductions for the both drugs were necessary in 18 (45%) patients due to severe neutropenia, anemia and thrombocytopenia. Chemotherapy administration was also delayed in 13 (32.5%) patients because of failure of hematologic recovery prior cycle of treatment. Treatment was discontinued early in 11 (27.5%) patients due to their requiring more than two dose reductions and long-term postponement of drug delivery.

Efficacy

The overall response rate was 35.0% (14 of 40; 95% CI: 20.6–51.7) with 3 (7.5%) complete and 11 (27.5%) PRs (Table 3). All three patients with a CR had M1a ($n = 2$) and M1b ($n = 1$).

Survival

At the time of last follow-up, 20 of the 40 patients enrolled had died of their disease. Median follow-up period of patients was 4.5 months (range 0.7–14.9 months). The median overall survival duration for all patients was 6.7 months (range 0.7–14.9 months) (Fig. 1). The 6-month overall survival was 57.4 ± 8.2%. The median survival for patients with responders (range 1.7–12.5 months) and stable (range 3.6–10.1 months) were not reached (Fig. 2). For progressed patients median survival was 2.1 months (range 0.7–14.9).

Discussion

We have demonstrated in the current study that the combination of temozolomide + fotemustine has substantial

Table 3 Response evaluation

Response	*n* (%)	95% CI
Complete	3 (7.5)	1.6–20.4
Partial	11 (27.5)	14.6–43.9
Stable	7 (17.5)	7.3–32.8
Progression	19 (47.5)	31.5–63.9

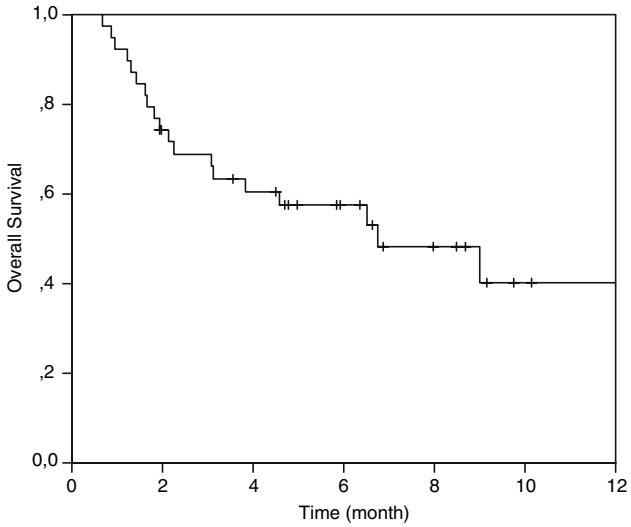

Fig. 1 The curve of overall survival of all patients treated with temozolomide + fotemustine chemotherapy

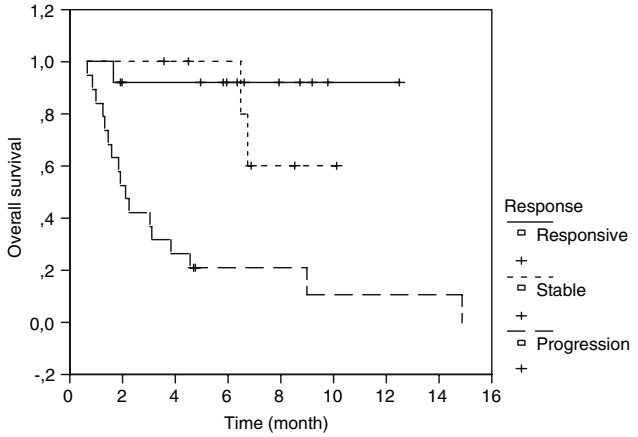

Fig. 2 The curves of overall survival of patients depending on response to temozolomide and fotemustine combination chemotherapy

antitumor activity in patients with advanced melanoma. As compared to monotherapy with temozolomide or fotemustine, concurrent delivery of both drugs may enhance antineoplastic activity from nearly 20 to 35% of patients in our study. In other words, this response rate represents a 75% increase in response rates compared with temozolomide or fotemustine alone in previously reported phase II trials.

In disagreement with the increases in response rate, survivals of patients were not increased, median 6 months. This inferior result in terms of overall survival in our study could perhaps be explained by the fact that a significant percentage of patients had extensively widespread; 70% of patients had M1c and multiple metastatic sites and short follow-up of the patients in the study.

As expected, this regimen was also found to have acceptable toxicity and adverse events were moderate to severe in patients. Myelosupression, particularly severe thrombocytopenia and neutropenia, was the principal dose-limiting toxicity of the combination treatment. Compared to temozolomide and fotemustine alone, the combination of these drugs appeared to enhance the frequency of myelotoxicity, which were the principal toxicities [14, 16–19]. However, other nonhematologic adverse effects were found not to be increased [18]. The myelosupressive complications were frequent and severe, however, readily manageable. Likewise, only one febrile neutropenia episode was encountered. Myelosupression-related treatment delay, dose reduction and therapy discontinuation occurred in significant numbers of the patients. No treatment-related death was noted. Therefore, in our study the combination with temozolomide and fotemustine has not been quite well tolerated, as had been with the cases in the studies. Therefore, we supposed that the dose and schedule of treatment used in the current study might be reasonable but less tolerable in the treatment of the patients with advanced melanoma.

The results of many experimental and clinical studies have indicated that AGAT activity is an important indicator of tumor sensitivity to several types of DNA-damaging agents, which target the O^6 position of guanine [14–17]. Therefore, strategies directed at inactivating AGAT may enhance the antitumor activity, and possibly the therapeutic indices of relevant anticancer agents in malignant tissue like melanoma, particularly those resulting in preferential AGAT inactivation. The rationale for the present study is the high rate of anticancer activity treatment of patients with melanoma with more protracted, low-dose temozolomide schedule. It depends on the hypothesis that the administration of temozolomide on protracted schedules may progressively lead to greater incativation of AGAT and inhibition of recovery of AGAT activity [14, 15]. Therefore, this situation may lead to auto-enhance the cytotoxicity of DNA damaging agents.

As part of protocol based on the AGAT-depletion rationale, fotemustine has been used in combination with DTIC for the treatment of metastatic melanoma and the use of sequential DTIC prior to fotemustine [18, 19] was examined. DTIC markedly reduced peripheral blood mononuclear cells AGAT and this effect occurred rapidly and also led to prolonged AGAT inactivation. Other investigators documented that AGAT remained inactivated after 7 days without temozolomide treatment and only partially recovered after 3 weeks from dosing [15]. Sequential association of temozolomide with nitrosoureas has shown promising antitumor activity in mice [20]. In human, Marzolini et al. [16] presented the first report of the pharmacokinetics of temozolomide given sequentially with fotemustine and Gander et al. [17] also reported the results of a dose-finding study of combination with temozolomide followed by fotemustine. We planned the schema of this study based on these data and Tolcher's findings [15]. Based on Tolcher's study [15], on the sustained inactivation of AGAT 7 days after treatment with temozolomide on the protracted schedule evaluated, we used temozolomide at a dose of 125 mg/day for 7 days every 3 weeks because of rapid, marked, and sustained AGAT inactivation. Additionally, fotemustine given at 4 h after temozolomide treatment does not seem to have much of an effect on temozolomide pharmacokinetics [16].

The rationale for combining temozolomide with fotemustine was based on the different mechanisms of cytotoxic action, and potential for improved antitumor activity compared with temozolomide alone. Fotemustine activity correlates inversely with AGAT activity [15–17] and temozolomide may affect AGAT activity [14, 15]. Based on this study experience, we conducted the present study. To our knowledge, this is the first clinical based in vivo report of temozolomide given sequentially with fotemustine.

In conclusion, temozolomide combined with fotemustine is an active and acceptably tolerated first-line

chemotherapy regimen in patients with metastatic melanoma. This combination seems to be promising for future studies.

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