Randomized Phase III Study of Temozolomide Versus Dacarbazine in the Treatment of Patients With Advanced Metastatic Malignant Melanoma

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***Purpose*: To compare, in 305 patients with advanced metastatic melanoma, temozolomide and dacarbazine (DTIC) in terms of overall survival, progression-free survival (PFS), objective response, and safety, and to assess health-related quality of life (QOL) and pharmacokinetics of both drugs and their metabolite, 5-(3-methyltriazen-1-yl)imidazole-4-carboximide (MTIC).**

***Patients and Methods*: Patients were randomized to receive either oral temozolomide at a starting dosage of 200 mg/m^2/d for 5 days every 28 days or intravenous (IV) DTIC at a starting dosage of 250 mg/m^2/d for 5 days every 21 days.**

***Results*: In the intent-to-treat population, median survival time was 7.7 months for patients treated with temozolomide and 6.4 months for those treated with DTIC (hazards ratio, 1.18; 95% confidence interval [CI], 0.92 to 1.52). Median PFS time was significantly longer in the temozolomide-treated group (1.9 months) than in the DTIC-treated group (1.5 months) (*P* = .012; hazards ratio, 1.37; 95% CI, 1.07 to 1.75). No major difference in drug safety was observed. Temozolomide was well tolerated and produced a noncumulative, transient myelosuppression late in the 28-day cycle. The most common nonhematologic toxicities were mild to moderate nausea and vomiting, which were easily managed. Temozolomide therapy improved health-related QOL; more patients showed improvement or maintenance of physical functioning at week 12. Systemic exposure (area under the curve) to the parent drug and the active metabolite, MTIC, was higher after treatment with oral temozolomide than after IV administration of DTIC.**

***Conclusion*: Temozolomide demonstrates efficacy equal to that of DTIC and is an oral alternative for patients with advanced metastatic melanoma.**

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THE INCIDENCE OF melanoma has increased approximately three-fold during the last 40 years, although this rate of increase has begun to slow.[1] Despite recent important developments in adjuvant treatment for stage III tumors, little has changed in the management of advanced metastatic disease.

A number of chemotherapeutic agents have activity in patients with metastatic melanoma, including dacarbazine (DTIC), the nitrosoureas, platinum analogs, vinca alkaloids, and the taxanes. Of these, DTIC has been the standard chemotherapeutic agent for melanoma.[2] In clinical studies, the response rate observed with single-agent DTIC chemotherapy ranges from 15% to 25%. Complete responses are rare (5% of cases) and short in duration (3 to 6 months). No multiagent chemotherapy, such as the Dartmouth regimen, has yet proved superior to single-agent DTIC chemotherapy in phase III clinical studies.[2-4] The combination of chemotherapy with biologic response modifiers has increased the response rate, but this has not resulted in improved survival, although a number of promising regimens are now being tested in phase III studies.[5]

The number of agents that are active in patients with metastatic disease is limited; currently, cure is not a realistic objective for treatment at this stage.[6,7] Median survival time for patients with stage IV disease is approximately 6 months, and the estimated 5-year survival rate is only 6%. Novel treatments for this disease are urgently needed. Because chemotherapy remains palliative, any improvement in tolerability of treatment or ease of treatment delivery is welcome.

Temozolomide is a novel oral alkylating agent with a broad spectrum of antitumor activity and relatively little toxicity. Both temozolomide and DTIC are prodrugs of the active alkylating agent 5-(3-methyltriazen-1-yl)imidazole-4-carboximide (MTIC). Unlike DTIC, which requires met-

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abolic activation, temozolomide spontaneously converts to MTIC under physiologic conditions.[8] Cytotoxicity of temozolomide seems to be mediated principally through methylation of DNA at the O^6 position of guanine,[9-11] although other mechanisms have been proposed.[12]

Temozolomide has demonstrated 100% oral bioavailability[13] and extensive tissue distribution, including penetration of the blood-brain barrier and the CSF.[14-16] In clinical studies, temozolomide was well tolerated and demonstrated rapidly reversible, mild to moderate myelosuppression. Notable activity was observed against recurrent glioblastoma multiforme, recurrent anaplastic astrocytoma, advanced malignant melanoma, and other refractory cancers.[13,17-19]

In a phase II study of temozolomide therapy in advanced metastatic melanoma conducted by the Cancer Research Campaign, the objective response rate was 21% (12 of 56 patients) and median survival time was 5.5 months.[20] The study population included many patients with adverse prognostic indicators, such as disease progression while receiving prior therapy or CNS metastases. This study suggested that temozolomide was likely to have efficacy at least equivalent to that of DTIC.

The primary objective of the current study was to compare overall survival of patients with advanced melanoma treated with either temozolomide or DTIC and to confirm the safety and tolerability of temozolomide. Secondary objectives included comparisons of progression-free survival (PFS), health-related quality of life (QOL), and response rates with either treatment.

PATIENTS AND METHODS

Patients

Patients at least 18 years of age with histologically confirmed, surgically incurable or unresectable, advanced metastatic melanoma were eligible for the study. Either a diagnosis of metastatic malignant melanoma had to have been made within 3 months of initiation of treatment with one of the study drugs or patients had to have symptomatic metastatic malignant melanoma or documented evidence of disease progression. Patients were required to have measurable disease. Also required were adequate performance status (World Health Organization status 0, 1, or 2) and renal (creatinine level $<$ 1.5 times the upper limit of normal [ULN]), hepatic (total bilirubin level $<$ 1.5 times ULN, AST level $<$ three times ULN, alkaline phosphatase level $\leq$ three times ULN), and bone-marrow (absolute neutrophil count $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000/mm^3, hemoglobin level $\geq$ 10 $\times$ g/dL) functions. Patients who had received previous treatment for metastatic disease other than local radiation therapy were not enrolled. Patients with relapsing disease requiring systemic chemotherapy after isolated limb perfusion (but not with DTIC) were eligible. A single regimen of adjuvant biologic therapy was also acceptable. Prior treatment had to have been completed at least 4 weeks before administration of a study drug.

Excluded from the study were pregnant or nursing patients; patients with nonmeasurable disease, ocular melanoma, or CNS metastases (observed on a magnetic resonance image); those who had not recovered from previous treatment or who had previous or concurrent malignancies at other sites; patients with disorders that would interfere with oral intake of the study drug; and patients with infections requiring systemic antibiotic therapy or with other indications of poor medical risk. Local ethical review committees approved the study.

Treatment

Patients were randomized to receive either temozolomide or DTIC. Treatment groups were stratified by major sites of disease, sex, and performance status. Temozolomide was administered orally under fasting conditions once a day for 5 consecutive days at a starting dose of 200 mg/m^2 (total dose per cycle, 1,000 mg/m^2). Treatment cycles were repeated every 28 days in the absence of disease progression or toxicity. DTIC was administered intravenously (IV) as a 30-minute infusion once a day for 5 consecutive days at a starting dose of 250 mg/m^2, and treatment cycles were repeated every 21 days. The dose was reduced by 25% of the starting dose when grade 3 or 4 hematologic toxicity (National Cancer Institute common toxicity criteria [NCI-CTC] [21]) occurred (in patients treated with temozolomide) or if retreatment was delayed for 2 weeks or more (in patients treated with DTIC). A 50% dose reduction was required in cases of grade 3 or 4 nonhematologic toxicity (NCI-CTC). Patients requiring more than two dose reductions were removed from the study. Retreatment was allowed once the absolute neutrophil count was $\geq$ 1,500/mm^3 and the platelet count was $\geq$ 100,000/mm^3. Up to 12 cycles of treatment were permitted (selected patients received more at the discretion of individual investigators).

Evaluations

A prestudy evaluation was completed within 2 weeks of a patient's receiving the study drug. Patients underwent clinical examination, determination of complete blood count, and biochemical analysis during every treatment cycle. A formal radiologic evaluation of disease was performed every second cycle. Responses were assessed using World Health Organization response criteria.[22] The severity of adverse events was assessed using NCI-CTC.

Health-Related QOL

Health-related QOL was assessed using the self-administered European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ)–C30 questionnaire.[23] The QLQ-C30 includes nine scales—one global QOL scale, five function scales (physical, role, emotional, cognitive, and social), and three symptom scales (fatigue, pain, and nausea and vomiting)—and questions on six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact). Higher scores on the function scales indicate better functioning and QOL, whereas higher scores on the symptom scales indicate the presence of more symptoms. The health-related QOL questionnaire was administered on day 1 of cycle 1 and after completion of each subsequent treatment cycle.

Pharmacokinetics

To determine the plasma concentrations of temozolomide, DTIC, and the active metabolite MTIC, we collected blood samples (5 mL) at various times before and after administration of each drug on day 4 during the first treatment cycle. Temozolomide, DTIC, and MTIC

concentrations were determined as previously described.[24,25] Pharmacokinetic analyses were performed using model-independent methods.

Statistical Methods

The primary objective of the study was to compare overall survival of patients in the intent-to-treat (ITT) population who were assigned either temozolomide or DTIC. Secondary objectives were to assess the time to progression, objective response rate, and QOL for the two treatments. The sample size was chosen to allow detection of a 3-month difference in median survival time between treatments with 80% power at the 5% level of significance (two-tailed), assuming a median survival time of 6 months in the control arm. Kaplan-Meier estimates of overall survival were generated, and the survival curves were compared using the log-rank test. Time to progression was also compared using the log-rank test. The effect of prognostic factors on survival and time to progression was examined using Cox regression. Mean changes from baseline in health-related QOL scores were compared for all patients as well as for clinical responders (complete responders and partial responders). Group differences in the change of QOL scores for each of the individual scales were tested during cycle 1 and at 12 weeks (during cycle 3 in the temozolomide treatment group and during cycle 4 in the DTIC treatment group) using *t*-test statistics. This analysis was limited to these time points because of a high drop-out rate beyond 12 weeks. The χ^2 test was used to compare the maintenance of or improvement in QOL scores from baseline to 12 weeks.

RESULTS

Patients

Between July 16, 1995, and February 25, 1997, 305 patients were enrolled at 34 centers worldwide. Of those, 156 patients were randomized to receive temozolomide and 149 to receive DTIC. Ten patients assigned to temozolomide therapy and eight to DTIC treatment proved ineligible. Of these patients, five had CNS metastases, four had no evidence of metastatic disease, four had previously undergone therapy for metastatic disease, two had concurrent malignancies, one had a second presentation of metastatic melanoma, one had an inadequate performance status, and one patient had insufficient diagnostic data. The remaining 287 patients (146 in the temozolomide treatment group and 141 in the DTIC treatment group) made up the eligible patient population, defined as those patients with untreated, advanced metastatic melanoma and no CNS involvement. Of these patients, 280 (144 in the temozolomide-treated group and 136 in the DTIC-treated group) received one dose of a study drug and made up the treated eligible population. Of the seven patients who did not receive a study drug, the condition of four deteriorated unexpectedly after randomization and three withdrew their consent.

Patient demographics were similar for each treatment group (Table 1). There were no significant differences in age, sex, performance status, or disease site at baseline between the treatment groups. The median time from initial diagnosis to development of metastatic disease was 22.4 months for the temozolomide treatment group and 20.8 months for the DTIC treatment group ($P = .67$).

Table 1. Patient Demographics

	Temozolomide Treatment Group (n = 156)		DTIC Treatment Group (n = 149)		
	No. of Patients	%	No. of Patients	%	*P*
Age, years					.71
Median	58.5		58.8		
Range	21-82		24-88		
Sex					.13
Male	98	63	80	54	
Female	58	37	69	46	
WHO performance status					.74
0	90	58	78	52	
1	51	33	56	38	
2	13	8	14	9	
3	1	0.6	0		
Not reported	1	0.6	1	0.7	
Disease site					
Skin and soft tissue	37	23.7	31	20.8	
Lung	32	20.5	34	22.8	
Viscera (nonhepatic)	32	20.5	33	22.1	
Liver	51	32.7	51	34.3	
Not recorded	4	2.6	0		
Time from initial diagnosis to metastatic disease, months					.67
Median	22.4		20.8		
Range	0-287		0-213		

Abbreviations: WHO, World Health Organization.

Survival

In the ITT population, median overall survival time among patients assigned temozolomide was 1.3 months longer than among those assigned DTIC (7.7 months versus 6.4 months), with a hazards ratio of 1.18 (95% confidence interval, 0.92 to 1.52) (Fig 1). Although the difference between the treatment groups was not significant ($P = .20$), the 95% confidence interval for the hazards ratio indicates that in terms of overall survival, the efficacy of temozolomide was, statistically, at least equivalent to that of DTIC. The trend favoring temozolomide was also observed in subpopulation analysis. Median survival time was 2 months longer for temozolomide-treated patients than for DTIC-treated patients in the treated eligible population (7.9 *v* 5.7 months; $P = .054$). The maximum survival difference (hazards ratio, > 1.3) was observed between 3 and 6 months, and there was a trend in favor of a better 6-month overall survival rate with temozolomide (61% *v* 51%; $P = .063$).

Median PFS time was significantly improved with temozolomide therapy (1.9 *v* 1.5 months; hazards ratio, 1.37;

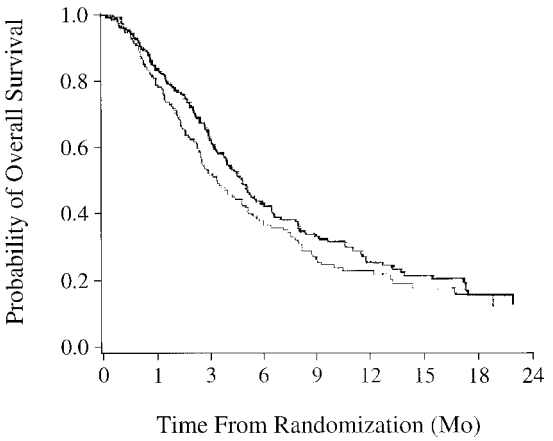

Fig 1. Overall survival in the temozolomide (thick line) and DTIC (thin line) treatment groups.

$P = .012$) (Fig 2). The difference in PFS favoring temozolomide was observed at as early as 4 weeks, with a maximum difference observed at 6 weeks. At this time, 34% of the patients receiving temozolomide and 48% of those receiving DTIC had disease progression. However, DTIC-treated patients underwent the first formal assessment for disease progression 2 weeks earlier than did temozolomide-treated patients, which may have contributed to the difference observed in PFS.

A Cox regression analysis was performed to identify possible prognostic factors for overall survival and PFS. Significantly longer ($P \leq .05$) overall survival and PFS were associated with two variables: site of metastatic disease ($P < .01$) and baseline performance status ($P < .01$). The magnitude of the effect associated with treatment remained virtually unchanged for both efficacy measures for age, sex, time from initial diagnosis to development of metastatic disease, and time from development of metastatic disease to randomization. This demonstrates that the treatment effect in the primary analysis of overall survival and PFS was not influenced by other prognostic factors. Subgroup analysis based on prognostic and demographic criteria supports the trend favoring temozolomide, as indicated by a hazards ratio of more than 1 in most subgroups (Table 2).

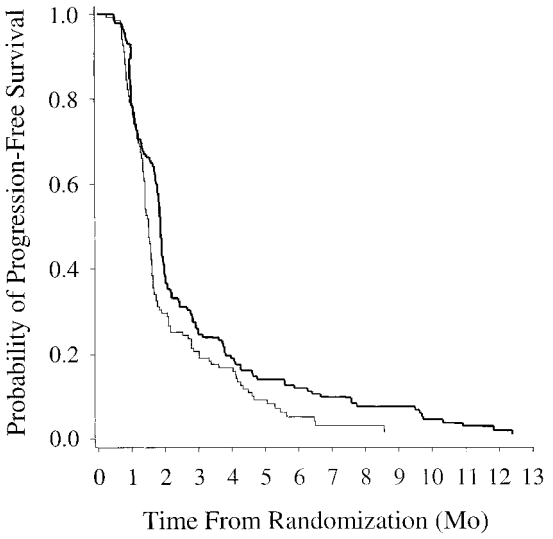

Fig 2. PFS in the temozolomide (thick line) and DTIC (thin line) treatment groups.

Response to Treatment

The response rates to the two drugs were similar (Table 3). Assessment of objective response in the ITT population showed that a complete response was achieved by 3% of both the temozolomide-treated (four of 156) and the DTIC-treated (four of 149) groups. Of the patients who were assigned temozolomide, 13.5% (21 of 156) showed an objective response to treatment, compared with 12.1% (18 of 149) of those assigned DTIC. Rates of disease stabilization were also similar between the two groups.

Among the responding patients (complete responders and partial responders), median overall survival time was 20 months in the DTIC treatment group but had not been reached at the conclusion of the study for the temozolomide treatment group. Duration of response was longer in the temozolomide treatment group; 18 of the 21 temozolomide-treatment responders survived longer than 12 months, compared with only 11 of the 18 DTIC-treatment responders. At the time we ceased collecting clinical data, 62% (13 of 21) of temozolomide-treated patients remained alive, compared with 39% (seven of 18) of DTIC-treated patients.

Safety

Of the 305 patients randomized in the ITT population, five patients in the temozolomide treatment group and seven in the DTIC treatment group did not receive at least one dose of study medication because of disease-related complications, failure to meet eligibility criteria, withdrawal of consent, or disease progression. The remaining 293 patients made up the safety population (151 in the temozolomide treatment group and 142 in the DTIC treatment group). A median of two cycles of treatment were administered in both treatment groups; 581 cycles of temozolomide therapy were administered to 151 patients, of which 24 cycles were at reduced doses. Dose reductions were less common in the DTIC treatment arm, with only 10 such instances across 501 cycles in the 142 patients. The proportion of delayed cycles

Table 2. Median Overall Survival By Subgroup of the Intent-to-Treat Population

	Median Overall Survival (months)				
	Temozolomide Treatment Group	DTIC Treatment Group	P*	Hazards Ratio	95% CI
Overall survival	7.7	6.4	.20	1.18	0.92-1.52
Age					
<50 years	7.8	6.2	.26	1.31	0.82-2.11
50-65 years	7.0	5.9	.77	1.06	0.72-1.57
>65 years	8.7	6.6	.60	1.13	0.72-1.78
Sex					
Male	7.7	5.6	.17	1.26	0.91-1.77
Female	7.7	6.8	.72	1.07	0.73-1.58
Baseline ECOG performance status					
0	9.8	8.3	.28	1.21	0.85-1.73
1	5.5	5.5	.83	1.05	0.70-1.57
2	2.7	2.1	.78	1.12	0.49-2.56
Site of metastatic disease					
Hepatic and any other	6.0	5.7	.82	1.05	0.68-1.62
Subcutaneous only	15.0	13.7	.96	0.97	0.32-2.92
Other	8.1	6.4	.16	1.3	0.91-1.74

Abbreviation: CI, confidence interval.

*Comparison between the two treatment arms.

was 6% for both treatments. Most of the delays and dose reductions occurred as a result of hematologic toxicity.

Both treatments were well tolerated, with most adverse events being mild to moderate in severity. For all cycles, the percentage of patients reporting any treatment-emergent adverse event, regardless of severity, was similar (92% in the temozolomide treatment arm and 87% in the DTIC treatment arm). The percentage of patients reporting grade 3 or 4 adverse events was also similar (38% in the temozolomide-treated group and 36% in the DTIC-treated group). The only exception was the percentage of patients reporting pain, which was higher in the DTIC treatment group (13% *v* 7%) (Table 4).

The most frequent adverse events observed with temozolomide therapy were nausea (52%), vomiting (34%), pain (34%), and constipation (30%) (Table 4). In the DTIC-treated patients, pain (39%), nausea (38%), constipation (29%), and vomiting (24%) were most common. Nausea and vomiting were easily controlled with standard antiemetics.

Table 3. Response to Treatment

	Temozolomide Treatment Group (n = 156)		DTIC Treatment Group (n = 149)	
	No.	%	No.	%
Complete response	4	2.6	4	2.7
Partial response	17	10.9	14	9.4
Stable disease	28	17.9	24	15.8
Progressive disease	95	60.9	94	63.1
Not treated/ineligible	12	7.7	13	8.7
Complete/partial response	21	13.5	18	12.1

Treatment-emergent hematologic toxicity (ie, events leading to study drug discontinuation, hospitalization, or transfusion) was also similar for each treatment group and included thrombocytopenia, leukopenia or neutropenia, and anemia. Thrombocytopenia occurred in 9% of both treatment groups. Leukopenia occurred in 2% of temozolomide-treated patients and 1% of DTIC-treated patients, whereas anemia occurred in 8% of temozolomide-treated patients and 11% of DTIC-treated patients (Table 5).

The percentage of cycles resulting in grade 3 or 4 thrombocytopenia (NCI-CTC) was 11% in the temozolomide treatment group and 7% in the DTIC treatment group, and the percentage of cycles resulting in grade 3 or 4 neutropenia (NCI-CTC) was 11% in the temozolomide treatment group and 13% in the DTIC treatment group. Myelosuppression was not cumulative and occurred in the first three cycles of treatment, with nadir platelet and neutrophil counts occurring late in the 28-day cycle. Recovery from the nadir occurred rapidly, usually within 9 days. Subgroup analysis revealed that sex and age had no clinical effect on the incidence of patients reporting at least one adverse event or grade 3 or 4 adverse events. There were few nonhematologic grade 3 or 4 adverse events.

The percentage of patients who discontinued the study because of adverse events was small in each group (3% of the temozolomide-treated group and 5% of the DTIC-treated group). There were 24 deaths during treatment, of

Table 4. Major Nonhematologic Adverse Events During All Cycles

Adverse Event	Temozolomide Treatment Group (%)			DTIC Treatment Group (%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Asthenia	12	3	0	14	1	0
Fatigue	20	3	0	18	2	0
Fever	11	1	1	18	2	0
Headache	22	5	1	12	1	0
Pain	34	7	0	39	13	0
Anorexia	15	0	0	20	2	0
Constipation	30	3	0	29	3	0
Nausea	52	4	0	38	4	0
Vomiting	34	4	1	24	4	0
Somnolence	12	0	0	13	1	0

which 18 were due to disease progression. Three patients taking temozolomide died from adverse events: one from a cerebral hemorrhage while thrombocytopenic, another from cerebral hemorrhage in the absence of thrombocytopenia, and the third from coma, in which a relationship to the drug could not be excluded. In the DTIC treatment group, one patient died from intestinal perforation with peritonitis, a second died from bowel ischemia, and a third died at home from unknown causes. None of these deaths were attributed to the chemotherapy.

Health-Related QOL

Baseline QLQ-C30 scores were available for 251 of the 305 patients. Of these, 224 had data at baseline and at the time of cycle 1. At 12 weeks, data were available for 50 temozolomide- and 31 DTIC-treated patients. Disease progression and death were the primary reasons for discontinuing the QOL study. At baseline, function and symptom scale scores were similar for the two treatment arms, and no statistically significant differences were observed in the QLQ-C30 scores. This was also the case at the end of the first cycle of treatment. At 12 weeks, however, statistically significant differences favoring the temozolomide-treated group were observed for physical functioning, fatigue, and insomnia. No significant differences between groups were observed for the remaining QLQ-C30 scores. Analysis of QLQ-C30 scores in responder subgroups (complete responders and partial responders) revealed similar results. At 12 weeks, responders in the temozolomide treatment group reported significantly better physical functioning and less insomnia than did responders in the DTIC treatment group. Comparison of the groups in terms of maintenance of or improvement in QLQ-C30 scores from baseline to 12 weeks indicated a significant advantage in the physical and cognitive functioning domains for the temozolomide-treated group compared with the DTIC-treated group (Table 6).

Pharmacokinetics

Pharmacokinetic evaluation of each parent drug and the metabolite, MTIC, was performed in 17 patients in each treatment group. Temozolomide was rapidly absorbed and eliminated after oral administration, and DTIC was rapidly absorbed after IV administration. Similarly, the formation of MTIC from either temozolomide or DTIC was rapid; maximum plasma MTIC concentrations were noted at approximately the same time for both drugs. Although DTIC was given at a higher dose, the mean systemic exposure to MTIC was twice as high for oral temozolomide–treated patients as for IV DTIC–treated patients (Fig 3 and Table 7).

DISCUSSION

Chemotherapy for advanced melanoma remains largely palliative, and survival times after diagnosis are short. Numerous trials of single agents and combinations of chemotherapy have been performed, but DTIC remains the standard regimen. Our study confirms findings of phase II trials that temozolomide is at least as effective against

Table 5. Treatment-Emergent Hematologic Adverse Events During All Cycles

Adverse Event	Temozolomide Treatment Group (%)			DTIC Treatment Group (%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	8	1	1	11	0	1
Neutropenia	5	1	2	3	1	1
Thrombocytopenia	9	2	5	9	4	4

Table 6. Numbers and Percentages of Patients With Maintenance of or Improvement in QLQ-C30 Scores at Week 12

Scale	Temozolomide Treatment Group (n = 51)		DTIC Treatment Group (n = 31)	
	No./Total	%	No./Total	%
Physical functioning	43/50	86	21/31	68*
Role functioning	42/51	82	22/31	71
Cognitive functioning	49/51	96	24/31	77*
Emotional functioning	43/51	84	22/31	71
Social functioning	44/51	86	22/30	73
Global QOL	33/51	65	21/30	70

*$P < .05$.

melanoma as DTIC. The response rates seen with both drugs are at the lower end of the range previously reported, but this reflects the scrutiny of response in this trial. All potential responses (complete or partial) were reviewed centrally, resulting in the downgrading of some conditions to stable disease. In addition, all treated eligible patients were evaluated for response; in some studies in which higher rates were found, fewer than 70% of patients randomized were evaluated, compared with 92% of patients in our study.[26] The overall survival and PFS noted are in keeping with previously published results for both drugs.[3,20,27]

Median survival time for patients receiving temozolomide for advanced metastatic melanoma was 1.3 months longer than for those receiving DTIC. This study, though large by melanoma trial standards, was designed to detect a 50% increase in survival longer than the 6 months expected with DTIC therapy. Such a large difference in outcome may be unexpected or unlikely, given that both drugs exert their cytotoxic effect via the same intermediary, MTIC. Nevertheless, the exposure to MTIC differed according to the parent drug administered. Although DTIC was administered IV at a higher dose than that of temozolomide, the mean systemic exposure to MTIC was twice as high for temozolomide-treated patients as for the DTIC treatment group. This might explain any difference in outcome between the treatments, if the trend toward improved survival seen with temozolomide therapy is supported by further experience and based on exposure to MTIC. Retrospective analysis of various DTIC regimens suggests that prolonged administration may be slightly more effective than shorter schedules, and it is possible that this relates to increased exposure to MTIC.[2] However, there are no data to help elucidate whether mean systemic MTIC exposure is important in determining response to these chemotherapies.

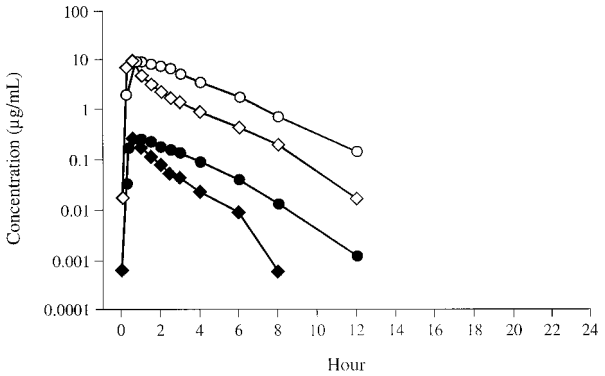

Fig 3. Serum concentrations of temozolomide (○), DTIC (◇), MTIC after temozolomide administration (●), and MTIC after DTIC administration (◆), all after dosing on day 4 of the first treatment cycle.

A statistically significant difference was observed in PFS, but the difference in the time to the first formal disease assessment between arms may have contributed to this discrepancy. However, when analysis was performed by subgroups based on demographics and disease-related criteria, overall survival and PFS were consistently better among patients treated with temozolomide than among those treated with DTIC. This trend was also observed in the treated eligible subpopulation. In addition, patients with metastatic malignant melanoma who achieved either a complete or partial response with temozolomide therapy survived longer.

No major differences were seen in the adverse events experienced by each treatment group, although more grade 1 or 2 nausea and vomiting occurred in the temozolomide-treated group. Similar levels of nausea and vomiting were seen in phase II trials of this drug, but, as in this study, the symptoms were usually mild and readily controlled.[19,27] No patient discontinued treatment because of these side effects. The difference in frequencies of nausea and vomiting between the two arms was apparent after only one cycle of treatment and is likely explained by the less frequent use of prophylactic serotonin ($5\text{-}HT_3$) antagonists in patients receiving temozolomide (69% *v* 79% in DTIC-treated patients). In later cycles of treatment, when $5\text{-}HT_3$ antagonist use was similar with both chemotherapies, the incidences of nausea and vomiting were also similar.

At the 12-week assessment point, patients who received temozolomide reported average improvements in physical functioning, fatigue, and insomnia. More temozolomide-treated patients (86%) than DTIC-treated patients (68%) had maintained or improved physical function scale scores. Additionally, patients who achieved a clinical response in the temozolomide treatment group showed greater improvements in health-related QOL scale scores for physical functioning and insomnia than did responders in the DTIC treatment group.

Table 7. Pharmacokinetics

	Temozolomide-Treated Patients (n = 17)		DTIC-Treated Patients (n = 17)	
	Mean	CV (%)	Mean	CV (%)
C_{max}, μg/mL	11.2	27	10.2	44
T_{max}, hours	1.06	58	0.50	25
AUC, μg/h/mL	34.4	13	16.0	69*
Half-life, hours	1.77	9	1.63	36*
CL/F, mL/min	189	20	592	43†
CL/F, mL/min/kg	2.50	16	8.88	34‡
Vd area/F, L	28.7	20	74.6	30†
Vd area/F, L/kg	0.378	13	1.100	24‡

Abbreviations: CV, coefficient of variation; C_{max}, maximum concentration; T_{max}, time of occurrence of peak concentration; AUC, area under the curve; CL, clearance; Vd, volume of distribution.

*n = 16.

†n = 15.

‡n = 14.

Temozolomide, which is 100% orally bioavailable,[13] allows for outpatient treatment. This is particularly desirable for patients with advanced melanoma, a group with a short life expectancy and a low rate of response to treatment. The oral formulation of temozolomide also makes prolonged schedules a possibility, as has recently been reported.[28] Six- and 7-week regimens have been shown to be feasible, and further studies are planned involving this agent in conjunction with radiation therapy in patients with glioma.

Temozolomide is schedule dependent, and the 5-day regimen used in this study is standard. However, given our knowledge of the mechanisms of resistance to temozolomide, the opportunity of improving the drug's efficacy exists. The DNA repair protein O^6-methylguanine-DNA methyltransferase (MGMT) is the principal mediator of resistance to O^6-alkylating agents such as temozolomide.[29] MGMT levels decrease after dosing with temozolomide as consequent DNA damage is repaired. By compressing the schedule, it may be possible to give subsequent doses of the drug when levels of MGMT are low, thereby prolonging exposure to the drug and MTIC to improve cytotoxicity and response rate. A 12-hour regimen has been tested, though not in melanoma patients, and clinical trials involving 4- and 8-hour schedules are under way.[30]

Patients with CNS metastases were specifically excluded from this study, but there is evidence that temozolomide penetrates the CNS.[15,16] The Cancer Research Campaign phase II study involving melanoma patients included four patients with intracerebral metastases, one of whom had a partial response to treatment.[20] This finding may point to an additional advantage of temozolomide over DTIC, and the treatment of CNS melanoma with temozolomide was the focus of a recently completed phase II trial.

Its acceptable safety profile and predictable pharmacokinetics make temozolomide an excellent candidate for inclusion in combination therapies for advanced metastatic melanoma. In a phase I study, the combination of oral temozolomide and subcutaneous interferon alfa-2b was evaluated in patients with histologically confirmed, surgically incurable metastatic melanoma.[31] In that study, temozolomide 150 mg/m^2/d in combination with interferon alfa-2b 7.5 MU/m^2 three times a week was well tolerated, and complete or partial remissions occurred in three of 12 patients. Temozolomide is now being tested in multidrug biochemotherapy regimens.

In conclusion, this study shows that in patients with advanced melanoma, treatment with temozolomide is associated with greater improvements in overall survival, PFS, and some QOL domains than is treatment with DTIC. The acceptable safety profile, QOL benefits, ability to penetrate the CNS, and ease of administration suggest that temozolomide could play an important role in the future management of this disease.

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