Temozolomide Plus Thalidomide in Patients With Advanced Melanoma: Results of a Dose-Finding Trial

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Purpose: **To establish a safe and tolerated regimen of an oral cytotoxic agent, temozolomide, and a cytostatic agent, thalidomide, in patients with unresectable stage III or IV malignant melanoma.**

Patients and Methods: **Patients with unresectable stage III or IV melanoma without brain metastases were entered successively onto four treatment cohorts: level 1, temozolomide 50 mg/m^2/d for 6 weeks followed by a 4-week break; levels 2, 3, and 4, temozolomide 75 mg/m^2/d for 6 weeks followed, respectively, by breaks of 4, 3, and 2 weeks. Thalidomide was started at 200 mg/d, and escalated to a maximum dose of 400 mg/d. Safety was assessed at weeks 2 and 4 and every 4 weeks thereafter; tumor response was evaluated every 8 to 10 weeks.**

Results: **Twelve patients were enrolled, three on each cohort. Therapy was generally well tolerated on all of the treatment schedules. Thalidomide at a dose of 400 mg/d was well tolerated in patients younger than 70, and 200 mg/d was well tolerated in older patients. The most common adverse events were grade 2 or 3 constipation and neuropathy, which were attributed to thalidomide. Five major responses (one complete, four partial) were documented, all at dose levels 2 to 4. Three of the five responding patients were in the over-70 age group. The median duration of response was 6 months (range, 4 to 17+ months), and the median overall survival was 12.3 months (range, 4 to 19+ months).**

Conclusion: **The combination of temozolomide and thalidomide was well tolerated and had antitumor activity in patients with advanced melanoma, including elderly patients over 70 years old.**

J Clin Oncol 20:2610-2615.

ONCE MELANOMA reaches advanced stages, it is usually incurable. Only 25% to 40% of patients with regional lymph node disease and less than 10% of patients with disseminated disease have long-term survival.

Dacarbazine (DTIC)-based regimens are considered the standard treatment for patients with unresectable stage III or IV disease.[1] Response rates with single-agent DTIC are low, however. Objective responses occur in 10% to 20% of patients, are complete in less than 5% of patients, and persist for a median of only 5 to 6 months. DTIC-containing combination chemotherapy regimens are no more effective, but are more toxic, than DTIC alone.[2] Although the addition of biologic agents, such as interleukin-2 and interferon alfa (IFNα), to chemotherapy results in a significantly increased response rate, biochemotherapy has not been shown yet to influence survival and is associated with severe toxicities.[3,4]

Temozolomide is an imidazole tetrazinone that was developed as an oral congener of DTIC. When administered on a 5-day dosing schedule every 4 weeks to patients with metastatic malignant melanoma, temozolomide-treated patients showed equivalent overall survival and improved progression-free survival compared with patients treated with DTIC alone.[5] In addition, unlike DTIC, temozolomide, which has shown activity against malignant astrocytoma,[6] crosses the blood-brain barrier.[7] This might be beneficial in melanoma, because CNS metastases are common and are a frequent cause of death.[8] Thalidomide is an orally bioavailable agent that possesses sedative, antiemetic, antiangiogenic, and immunomodulatory activities.[9-13] Thalidomide also has clinical activity against several cancers,[14] although no responses were observed among 17 patients with malignant melanoma treated at a dose of 100 mg daily.[15]

We hypothesized that the combination of cytotoxic therapy with a biologic modulator might be superior to cytotoxic therapy alone for advanced malignant melanoma. On the basis of pharmacokinetic considerations,[16] we hypothesized that administration of temozolomide on a daily, low-dose schedule might have advantages over intermittent, higher dose therapy. We therefore initiated a study to determine a tolerable dosing regimen of temozolomide, using an extended continuous schedule, in combination with thalidomide.

PATIENTS AND METHODS

Patients

Eligible patients were adults, age $\geq$ 18 years, with histologically confirmed, unresectable stage III or IV metastatic melanoma. Patients

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Submitted September 7, 2001; accepted March 14, 2002.

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0732-183X/02/2011-2610/$20.00

DOI: 10.1200/JCO.2002.09.034

Table 1. Treatment Regimen

Dose Level	Study Treatment	Week 1	2	3	4	5	6	7	8	9	10
1	Temozolomide, mg/m^2/d	50	50	50	50	50	50	—	—	—	—
	Thalidomide*										
	mg/d; < 70 years	200	200	300	300	400	400	400	400	400	400
	mg/d; ≥ 70 years	100	100	150	150	200	200	250	250	250	250
2	Temozolomide, mg/m^2/d	75	75	75	75	75	75	—	—	—	—
	Thalidomide	Same as dose level 1									
3	Temozolomide, mg/m^2/d	75	75	75	75	75	75	—	—	—	New cycle
	Thalidomide	Same as dose level 1									
4	Temozolomide, mg/m^2/d	75	75	75	75	75	75	—	—	New cycle	
	Thalidomide	Same as dose level 1									

*Thalidomide is escalated to a maximum dose of 400 mg/d (250 mg/d in patients age ≥ 70 years) administered continuously as tolerated.

were required to have measurable disease, no prior systemic chemotherapy for melanoma, no concurrent immunotherapy or radiotherapy, and a Karnofsky performance status ≥ 70%. Prior immunotherapy or radiotherapy was permitted, but must have been completed at least 4 weeks before study entry. Adequate organ function (absolute granulocyte count ≥ 1,500/mm^3; platelet count ≥ 150,000/mm^3; serum bilirubin and creatinine levels ≤ 1.5 times upper limit of normal; and AST, ALT, and alkaline phosphatase ≤ three times upper limit of normal) was required. Patients were excluded if they had any ongoing toxic effect from prior treatment, frequent vomiting or other condition that could interfere with the intake of oral medication, a history of active angina or myocardial infarction within 6 months or significant arrhythmia, grade ≥ 2 neurotoxicity, serious infections, concurrent malignancy or human immunodeficiency virus infection, general anesthesia within 2 weeks before starting treatment, or any immunotherapy or radiotherapy within 4 weeks of treatment. Patients with CNS metastases were excluded in order to avoid the confounding effects of CNS disease on the interpretation of thalidomide-induced neurologic toxicities. Pregnant or lactating women were ineligible, and a negative pregnancy test was required immediately before treatment for all women capable of becoming pregnant. All patients complied with the System for Thalidomide Education and Prescribing Safety program, including regular pregnancy testing and approved contraception during treatment with thalidomide. All patients gave signed informed consent. The protocol and consent form were reviewed and approved by the Memorial Sloan-Kettering Cancer Center institutional review board.

Treatment and Patient Evaluation

Temozolomide was given by mouth once daily for 6 weeks, followed by a 2- to 4-week break (total cycle length, 8 to 10 weeks) to permit recovery from any treatment-related toxicities. The maximum planned temozolomide dose of 75 mg/m^2/d was based on the results of an earlier phase I trial.[16] Thalidomide was administered by mouth once daily at bedtime on each day of the 8- to 10-week cycle. Patients were instructed to take thalidomide 30 to 60 minutes before temozolomide. The dosing schedule is shown in Table 1. The starting dose of thalidomide was 200 mg/d. The dose of thalidomide was titrated in 100-mg increments at 2-week intervals, to a maximum of 400 mg/d during the first treatment cycle and maintained at that dose as long as therapy was tolerated. After the first elderly patient (≥ 70 years old) in dose level 1 experienced grade 3 neurologic toxicity, the protocol was amended so that patients ≥ 70 years of age began thalidomide at a dose of 100 mg/d and escalated in 50-mg/d increments to a maximum of 250 mg/d. Thalidomide therapy was interrupted for grade 3 or 4 sedation, peripheral neuropathy and constipation, and/or grade 2 or 3 macular/papular rash. Thalidomide was restarted at the next lower dose level the patient had previously tolerated, or at 50 or 100 mg if the initial dose of 100 or 200 mg was not tolerated, when toxicity resolved to grade ≤ 1. Dose re-escalation was attempted when toxicity remained at ≤ grade 1 for at least 2 weeks.

Cohorts of three to six patients were planned at each dose level. If any of the first three patients at a given dose level experienced dose-limiting toxicity that was considered related to temozolomide, three additional patients would be enrolled at that level. If three of six patients at a given level experienced dose-limiting toxicity, enrollment at subsequent dose levels would not proceed. Grade 3 or 4 nonhematologic toxicities (except for the known thalidomide side effects of skin rash, constipation, peripheral neuropathy, and excessive sedation) and grade 4 hematologic toxicities were considered dose limiting. Toxicities were graded according to the National Cancer Institute common toxicity criteria.

At enrollment, a pathologist at Memorial Sloan-Kettering Cancer Center confirmed the histologic diagnosis. A complete history and physical examination, routine laboratory studies, ECG, and serum pregnancy testing were performed, and baseline radiographs and scans were obtained to document the extent of disease. During treatment, patients were monitored for signs of toxicity and adverse events with a history and physical examination (including neurologic examination).

Interim laboratory evaluations (complete blood count, comprehensive metabolic panel, and lactate dehydrogenase) were performed monthly. Disease measurements, including physical examination, radiography, scanning, and other diagnostic tests, were obtained at the end of each treatment cycle.

RESULTS

Patient Characteristics

Twelve eligible patients were enrolled, three at each dose level. Pretreatment characteristics and treatment outcomes are listed in Table 2. The median age was 69.5 years (range, 47 to 75 years) and the median Karnofsky performance status was 90% (range, 70% to 90%). Nine patients (75%) had disease at three or more sites (range, one to eight), most commonly lung, liver, soft tissue, and lymph nodes. The

Table 2. Summary of Patient Characteristics and Outcome

Dose Level	Sex/Age/PS	Site of Metastasis	Prior Therapy	No. of Cycles	OR	OS (months)	Status
1	M/59/90	Lung, liver, LN	S	1	MR	6	DOD
	M/75/80	Lung, liver, ST, LN	None	0	NA	4	DOD
	M/47/90	Lung	None	1	PD	18	DOD
2	F/69/80	Lung, LN	S, V	3	PR	17	DOD
	M/73/90	Cutaneous	None	3	CR	19+	NED
	M/75/80	Lung, ST, skin, LN	S	1	Mix	8	DOD
3	F/47/90	ST, skin, LN	S, V	3	PR	14	DOD
	M/67/90	Lung, ST, LN	S, V	2	PD	11	DOD
	M/70/70	Lung, liver, spleen, adrenal gland, Mesentery/omentum carcinomatosis, ST, malignant ascites, LN	None	2	PR	5	DOD
4	F/72/90	Lung, liver, bone, LN	None	3	PR	13	DOD
	M/61/90	Lung, liver, ST, skin, LN	V	1	PD	5	DOD
	M/73/80	Lung, ST, LN	S	1	SD	15+	AWD

Abbreviations: M, male; F, female; PS, Karnofsky performance status (%); LN, lymph nodes; ST, soft tissue; S, surgery; V, vaccine; OR, objective response; MR, minor response; NA, not assessable; PD, progressive disease; PR, partial response; CR, complete response; Mix, mixed response; SD, stable disease; OS, overall survival; DOD, died of disease; AWD, alive with disease; NED, no evidence of disease.

median number of treatment cycles was 1.5 (range, zero to three). One elderly patient (age 75) in dose level 1 was removed from the study after 1 month of treatment, before completing the first treatment cycle, because of persistent peripheral neuropathy despite discontinuation of thalidomide.

Toxicity

Treatment with the combination of temozolomide and thalidomide was generally well tolerated, with most toxicity limited to grade 2 (Table 3). Except for a single patient with grade 2 leukopenia, there was no hematologic toxicity. No patient required a reduction in the temozolomide dose. The most common toxicities were constipation, dyspnea, and peripheral neuropathy. The latter generally resolved after dose reduction or discontinuation of thalidomide. Constipation was usually controlled with the use of stool softeners and laxatives. After completing the first cycle of therapy, one patient developed a deep vein thrombosis and pulmonary embolism after prolonged car travel; the relationship of this event to treatment is unknown. Two patients discontinued thalidomide, one during the first cycle and one after the third cycle of therapy, because of peripheral neuropathy. The first of these patients was also an alcoholic, which may have predisposed him to thalidomide-induced neuropathy, although symptoms of peripheral neuropathy were mild before treatment.

Table 3. Summary of Toxicity

Toxicity	No. of Patients (N = 12)
Grade 2 leukopenia	1
Grade 3 DVT	1
Grade 4 PE	1
Grade 2/3 constipation	8/1
Grade 2 dyspnea	3
Grade 2/3 neuropathy	2/2
Grade 2/3 rash	1/1
Grade 2 nausea/vomiting	1/1
Grade 2 blurred vision	1
Grade 2 abdominal pain or cramping	1
Grade 2 dry skin	1
Grade 2 diarrhea	1
Grade 2 fatigue	1
Grade 2 headache	1
Grade 2 joint pain	1
Dose modification/discontinuation of thalidomide	6/3

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

One patient developed grade 3 skin rash after two cycles of therapy and was able to resume thalidomide at a lower dose after 1 month off treatment. Dose reduction allowed six additional patients to successfully continue thalidomide therapy (at doses of 50 to 200 mg/d).

Dose level 4 (temozolomide 75 mg/m^2/d for 6 weeks, followed by a 2-week break) was safe and well tolerated. The maximum dose of thalidomide achieved in each patient and the doses tolerated at the end of study are listed in Table 4. Thalidomide at a dose of 400 mg/d was well tolerated by patients less than 70 years of age. Five of the six patients tolerated dose escalation according to protocol. One of these five patients required a reduction in the thalidomide dose to 200 mg after 14 weeks; the sixth patient could not tolerate dose escalated beyond 200 mg/d and required eventual dose reduction to 50 mg/d. Of the six patients $\geq$ 70 years of age, three had their dose escalated to a maximum thalidomide dose of 250 mg/d and the three others to 200 mg/d. Only one

Table 4. Tolerated Doses of Temozolomide

Dose Level	Patient No.	Age (years)	Maximum Thalidomide Dose (mg/d)	Duration on Maximum Dose (weeks)	Dosage at End of Therapy (mg/d)
1	1	59	400	8	400
	2	75	200	4	200
	3	47	400	6	400
2	4	69	400	22	400
	5	73	250	26	250
	6	75	200	6	200
3	7	47	200	4	50
	8	67	400	14	200
	9	70	250	4	150
4	10	72	200	12	200
	11	61	400	4	400
	12	73	250	2	150

was able to tolerate continued treatment at 250 mg/d, however, whereas three of the remaining five patients tolerated doses of 200 mg/d for 4 weeks or more.

Response

Objective tumor regression was observed at dose levels 2, 3, and 4 (Table 5). Overall, there was one complete response, four partial responses, three patients with stable disease (including one minor response and two mixed response), and three with progressive disease. The median duration of response for patients with complete or partial response was 6 months (range, 4 to 17+ months). The median overall survival from initiation of treatment was 12.3 months (range, 4 to 19+ months); patients who achieved an objective response lived 5 to 19+ months. Of the 12 enrolled patients, two remain alive. One patient, who achieved a partial response in the lung, discontinued thalidomide after one cycle because of neurotoxicity. He was maintained, off study, on temozolomide alone, and is alive with near complete resolution of pulmonary metastases at 15+ months. Another patient who achieved a complete response discontinued treatment after three cycles because of peripheral neuropathy. He was also maintained off study on temozolomide alone, and is alive with no evidence of disease at 19+ months. Another patient, who developed progressive lung metastases after one cycle on dose level 1 but subsequently responded to treatment with a combination regimen that included temozolomide, survived 18 months.

Table 5. Response by Dose Level

Dose Level	CR	PR	SD	PD
1	—	—	1	1
2	1	1	1	—
3	—	2	—	1
4	—	1	1	1
Total	1	4	3	3

DISCUSSION

This trial demonstrates that temozolomide is well tolerated in combination with daily thalidomide. Severe hematologic toxicity did not occur, and other adverse events were relatively infrequent and rarely severe. The occurrence of moderate or severe constipation in three quarters of the patients and peripheral neuropathy in one third deserves comment, however. Although both are known complications of thalidomide therapy, the high incidence suggests the possibility that temozolomide may have augmented the autonomic and peripheral neuropathic effects of thalidomide. Indeed, constipation has been reported in studies of temozolomide, although it was rarely severe.[5,16] Although constipation was usually controlled by the regular use of laxatives and stool softeners and did not require dosage modification, the severity of peripheral neuropathy in some patients suggests that thalidomide dosage reduction should be considered for patients with grade 2 peripheral neuropathy.

This study was not designed to determine the maximum-tolerated dose of either thalidomide or temozolomide, because the maximum dose of both drugs was predefined. A reduction in temozolomide doses was not required in any patient, and a dose of 75 mg/m^2/d for 6 weeks, followed by either a 2-, 3-, 4-week break, was tolerated in all nine patients treated at this dose, irrespective of age. Five of six patients younger than age 70 were able to tolerate a thalidomide dose of 400 mg/d. Although our decision to limit the maximum thalidomide dose to 250 mg/d in patients aged 70 or more was admittedly derived from the experience in only a single patient, only one of the six patients in this age group was able to tolerate this dose level for over 4 weeks, whereas three tolerated a dose of 200 mg/d. Thus, it seems reasonable to recommend the temozolomide dose and schedule used in dose level 4 for phase II trials of the combination, with a maximum thalidomide dose of 400 mg/d for younger individuals and a maximum of 200 mg/d for those over 70.

Although demonstration of efficacy was not a primary aim of this study, it is noteworthy that responses were observed in each cohort of patients that received a temozolomide dose of 75 mg/m^2/d for 6 weeks (levels 2 to 4), and were durable in some patients. Also noteworthy is that half of the patients in this trial were 70 years of age or older, and were not felt to be suitable candidates for more toxic regimens. Although older patients were more sensitive than younger ones to the sedative effects of thalidomide, three of the five responding patients were in the over-70 age group.

Originally developed as a sedative, thalidomide has since been shown to possess antiangiogenic and other biologic modulatory properties. Thalidomide interrupts angiogenesis mediated by basic fibroblast growth factor (which is abundantly produced by melanoma cells),[9] upregulates expression of intercellular adhesion molecule-1 (implicated in metastasis) while downregulating E- and L-selectin and vascular cell adhesion molecule-1,[10] inhibits tumor necrosis factor alpha production,[11] induces production of Th1-type and Th2-type cytokines,[12] and costimulates $CD8^+$ and $CD4^+$ T-cell proliferative responses.[13] One or more of these activities may cause cytostasis and inhibition of tumor growth. When administered in combination with cytotoxic chemotherapy, cytostatic therapy may inhibit tumor regrowth and the development of resistant disease.[17]

Temozolomide is approved in the United States for treatment of refractory anaplastic astrocytoma; it is a prodrug that hydrolyzes to monomethyl triazenoimidazole carboxamide at physiologic pH.[18] Monomethyl triazenoimidazole carboxamide is the active metabolite of both temozolomide and DTIC. Its complete oral bioavailability and its ability to cross the blood-brain barrier[7] make it an attractive alternative to DTIC, which possesses neither of these properties. Temozolomide has shown activity against CNS metastases in melanoma and other malignancies.[19] This could be an advantage in melanoma, as CNS metastases are a frequent cause of death.[7] The results of several phase II/III trials in melanoma have demonstrated the activity and tolerability of temozolomide, alone or in combination with other drugs.[5,20-23] In one phase II trial, temozolomide was administered over 5 days at a dose of 200 mg/m^2 either alone or in combination with IFNα or thalidomide.[20] The preliminary results indicated that thalidomide in combination with temozolomide was better tolerated than either of the other two treatments. This combination caused significantly less myelosuppression than temozolomide either alone or in combination with IFNα, and significantly less diarrhea than temozolomide with IFNα, perhaps because of the known constipating side effect of thalidomide.

The current trial used an extended continuous dosing schedule of temozolomide, modeled on phase I results reported by Brock et al.[16] This schedule results in a 2.1-fold greater drug exposure over 4 weeks compared with the conventional 5-day dosing schedule. It has been postulated that this schedule might lead to improved antitumor activity by cumulative depletion of O^6-alkylguanine-DNA-alkyltransferase, a DNA repair enzyme involved in resistance of melanoma cells to DTIC.[24] Continuous dosing may also decrease the opportunity for development of resistant disease by minimizing the length of the intertreatment interval, during which tumor regrowth could occur. In addition, more chronic administration of low-dose chemotherapy may produce an antiangiogenic effect,[25] which may augment the activity of or act synergistically with other antiangiogenic agents, such as thalidomide.

Combining cytostatic and cytotoxic therapy is a new strategy in melanoma management. By treating both the endothelial cell and tumor cell components concurrently, the combination of cytotoxic and cytostatic therapies has the potential to induce prolonged dormancy and may be more effective than either strategy alone.[17,26] In our trial, the combination of temozolomide with thalidomide was well tolerated for up to 6 months and induced complete or partial tumor regression in five of nine patients who received a temozolomide dose of 75 mg/m^2/d. On the basis of these findings, a phase II study of this combination is currently ongoing in advanced malignant melanoma to further characterize toxicity and to establish its efficacy, stratified for patients with and without brain metastases.

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