

## Low-Dose Outpatient Chemobiotherapy With Temozolomide, Granulocyte-Macrophage Colony Stimulating Factor, Interferon- $\alpha$ 2b, and Recombinant Interleukin-2 for the Treatment of Metastatic Melanoma

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### A B S T R A C T

#### Purpose

The objective of this study was to further investigate the efficacy and safety of low-dose outpatient chemobiotherapy in patients with unresectable metastatic melanoma.

#### Patients and Methods

Thirty-one patients with histologically confirmed unresectable measurable metastatic melanoma were enrolled in an open-label, multicenter phase II study. The treatment regimen consisted of oral temozolomide followed by subcutaneous biotherapy with granulocyte macrophage colony-stimulating factor, interferon- $\alpha$ , and recombinant interleukin-2 (rIL-2).

#### Results

Twenty-eight patients (90%) had M1c disease, and 58% had three or more sites of metastasis. Four patients (13%), all with M1c disease, had a complete response, and four patients had a partial response. The median progression-free survival was 4.9 months and the median overall survival was 13.1 months. Two patients (6%) developed CNS metastasis as the first site of disease progression, and 7 (23%) of 30 experienced CNS progression after receiving chemobiotherapy. A total of 112 cycles of therapy were administered. Toxicity occurred in 78% of the cycles and was grade 1 or 2 in the majority of cases and easily managed. Grade 4 toxicity occurred in 3% of the cycles.

#### Conclusion

This low-dose chemobiotherapy combination produces clinical responses in patients with metastatic melanoma, even in those with M1c disease, is well tolerated, and allows home dosing. It offers a reasonable alternative to high-dose regimens, such as high-dose biochemotherapy or rIL-2 requiring prolonged periods of hospitalization, or single agent outpatient regimens, such as dacarbazine, which is usually not effective in patients with M1c disease. Furthermore, it may protect against the development of brain metastases.

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### INTRODUCTION

Patients with unresectable metastatic melanoma have a dismal prognosis. The disease responds poorly to currently available chemotherapies and biologic agents. The median survival in this patient population is 6 to 10 months and has not improved significantly in decades. Dacarbazine (DTIC) and high-dose intravenous bolus recombi-

nant interleukin-2 (rIL-2) are the only agents approved by the US Food and Drug Administration for therapy of patients with metastatic melanoma.

de Gast et al conducted trials of chemobiotherapy with temozolomide, granulocyte macrophage colony-stimulating factor (GM-CSF), low-dose rIL-2, and interferon- $\alpha$  (IFN- $\alpha$ ) in patients with

metastatic melanoma or renal cell carcinoma.<sup>1-3</sup> The rationale for this combination of cytokines for the biologic therapy component of the regimen is that they improve antigen presentation (GM-CSF), cause expansion and activation of T cells (rIL-2 + GM-CSF), increase effector-cell function (IFN), and cause immunosensitization of the tumor cells by increased expression of human leukocyte antigen, tumor-associated antigens, and adhesion molecules (IFN). de Gast et al<sup>3</sup> reported that the regimen is well tolerated, has toxicities manageable on an out-patient basis, and may have superior clinical benefit to that found currently approved therapies. We pursued evaluation of this regimen to gain additional information about its safety and efficacy.

## PATIENTS AND METHODS

### Patient Selection and Eligibility

Adult patients with histologically confirmed unresectable metastatic melanoma who met the following eligibility criteria were included in the study: Karnofsky performance score  $\geq$  70, adequate hematologic, liver, and renal function, and life expectancy greater than 12 weeks. Patients were permitted to have received therapy for prior disease but must have completed therapy at least 1 month before study entry. Patients with brain metastases were eligible provided that the brain metastases were controlled. Investigations were performed after approval by the local Human Investigations Committees of the participating institutions and patients gave written informed consent for participation in the study.

### Treatment Regimen

For the first treatment cycle, patients received oral temozolomide: 200 mg/m<sup>2</sup> (150 mg/m<sup>2</sup> daily for patients with a previous history of chemotherapy) daily for 5 days (Table 1). Since temozolomide is highly lipophilic, there was concern that use of the full calculated body-surface area (BSA) might lead to overdosing in obese subjects. Therefore, the dose of temozolomide was limited to a maximum BSA calculation of 2.0. The temozolomide treatment was followed by 12 daily subcutaneous injections of biotherapy starting on day 6. The biotherapy consisted of a combination of GM-CSF (125  $\mu$ g/m<sup>2</sup> to a maximum 250  $\mu$ g), IFN (5 MU), and rIL-2 (4 MU/m<sup>2</sup>). This was followed by an 11-day period of rest. This 28-day treatment cycle was repeated as clinically indicated with the same treatment sequence and dosage of each individual medication, or adjusted per-dosing modifications based on adverse

events and the investigator's judgment. Patients intolerant (experiencing grade 3 or grade 4 toxicities or at the investigator's discretion) of the biotherapy received a decreased dose of rIL-2 of 2 MU/m<sup>2</sup>. The dosage of temozolomide was adjusted on the basis of the nadir absolute neutrophil count and/or nadir platelet count. The dosages of GM-CSF and IFN were not adjusted. In the absence of disease progression or unacceptable toxicity, patients were permitted to continue to receive treatment with the protocol medications for up to eight treatment cycles from initial dose. At the investigator's discretion, patients continuing with at least stable disease or in response could be treated beyond eight cycles after discussion with the principal investigator.

### Response and Toxicity Assessments

Staging studies (with tumor measurements) were obtained within 28 days of the start of the first treatment cycle and then every other treatment cycle (approximately 56 days). Patients were removed from study for unacceptable toxicity or continued disease progression. Each serious adverse event was fully evaluated and, if it was drug related, a decision was made as to whether the risk/benefit warranted the patient's continuation in the study. Each serious adverse event was reported to the sponsoring company and the supervising institutional review board.

### CNS Metastases

During the course of this study, O'Day et al<sup>6</sup> reported results of their analysis of 163 patients treated with DTIC-based concurrent biochemotherapy regimen (DTIC, vinblastine, cisplatin, decrescendo IL-2, and IFN), pointing out that CNS progression occurs frequently in the setting of relative control of systemic disease and is the cause for a significant number of biochemotherapy treatment failures and death (unpublished data). Therefore, although the analysis was not planned in advance, we collected information on the incidence of CNS metastases in the patients during and following low-dose outpatient chemobiotherapy. In addition, we determined the timing of the appearance of CNS metastases relative to progression of disease elsewhere.

### Statistical Methods

This study was a phase II, open-label trial of chemobiotherapy for patients with unresectable metastatic melanoma. The study was intended to include 30 patients, but one additional patient was treated. All analyses were based on the intent-to-treat principle (ie, all study participants were included in the analyses, regardless of whether they violated protocol or completed the study). Only descriptive analyses of safety parameters were planned and conducted. Response and progression were evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee.<sup>4</sup> Patients were considered responders to this treatment regimen, if, by the end of the treatment period, they had achieved an objective response (either a partial response (PR) or complete response (CR) of at least 28 days duration). Time to progression (TTP) and survival were measured from day 1 of chemobiotherapy. The duration of progression-free and overall survival, TTP, and survival curves were generated using the Kaplan-Meier method.<sup>5</sup> The 95% CIs were calculated using Greenwood's formula for the SE. The incidence of CNS metastases in patients receiving

**Table 1.** Treatment Regimen: 28-Day Cycle

	Treatment	Dosage
Days 1-5	Temozolomide	200 mg/m <sup>2</sup> PO
Days 6-17	Biotherapy	
	Interferon- $\alpha$ 2b	5 MU SQ
	Interleukin-2	4 MU/m <sup>2</sup> SQ
	GM-CSF	125 $\mu$ g/m <sup>2</sup> SQ
Days 18-28	Rest	

Abbreviations: PO, orally; SQ, subcutaneously; GM-CSF, granulocyte macrophage colony-stimulating factor.

this low-dose, outpatient chemobiotherapy protocol was compared with the incidence of CNS metastases in patients receiving a high-dose inpatient biochemotherapy (O'Day et al, unpublished data) using Fisher's exact test. Univariate Cox proportional hazards models were run to evaluate the relationship among prior therapy, the duration of progression-free survival, and overall survival.

**RESULTS**

**Characteristics of the Study Population**

Thirty-one patients with unresectable stage IV melanoma were enrolled (Table 2). The majority of patients (90%) demonstrated stage M1c disease and 19 patients (58%) had three or more metastatic sites. The patient population included two patients who had brain metastases that were considered controlled at study entry.

**Table 2.** Baseline Patient Characteristics (N = 31)

Variable	No.	%
Sex		
Female	8	26
Male	23	74
Age, years		
Median	58	
Range	26 to 85	
< 55	11	35
≥ 55	20	65
Karnofsky performance score		
100	17	55
90	11	35
80	2	6
70	1	3
Prior therapy		
Chemotherapy	2	6
Biotherapy	13	42
GM-CSF	8	26
rIL-2	0	
Interferon	3	10
Other	2	6
Elevated LDH	15	48
Missing value	2	6
Stage		
M1a (subcutaneous and/or lymph node metastases only)	1	3
M1b (lung metastases only)	2	6
M1c (all other viscera or metastases with elevated LDH)*	28	90
Lung	21	67
Lymph node	16	52
Liver	15	48
Bone	6	19
Subcutaneous	5	16
Spleen	2	6
Adrenal	2	6
Bowel	2	6
Brain	2	6
Other (ovary, kidney, pancreas, abdominal mass, mucosal)	5	16
No. of disease sites (organs)		
1	7	23
2	6	19
≥ 3	18	58

Abbreviations: GM-CSF, granulocyte macrophage colony-stimulating factor; rIL-2, recombinant interleukin-2; LDH, lactate dehydrogenase.  
 \*Percentages may add to > 100% because patients may have more than one site of metastatic disease.

**Chemobiotherapy**

A total of 112 cycles of chemobiotherapy were administered, ranging from 0 to 13 cycles with a median of four cycles administered per patient. Two patients completed less than one full cycle of chemotherapy; one patient because of rapid disease progression and the other because of an adverse event (grade 3 cardiac arrhythmia, supraventricular tachycardia). Three additional patients completed only one cycle of therapy. One patient was responding to therapy but treatment was discontinued because of an adverse event (grade 4 psychosis requiring hospitalization). It was thought that the psychosis might be related to the biologics he was receiving as part of the therapeutic regimen. The other two patients discontinued treatment because of disease progression. The remaining 26 patients completed at least two cycles of therapy. One patient continued to have evidence of disease activity and tolerated treatment well with a 100% performance status while maintaining an unusually heavy workload. He had an intense desire to continue treatment and completed 13 cycles of therapy. Three patients were taken off protocol and placed on maintenance biotherapy with GM-CSF and rIL-2<sup>6</sup> because they had achieved their maximum response to treatment on the protocol (CR, PR, or stable disease), which remained unchanged with subsequent cycles of chemobiotherapy. All patients were evaluated for response and toxicity, including those who completed less than one full course of chemobiotherapy.

**Response**

Four patients (13%) achieved a CR and four patients (13%) had a PR (Table 3). Thus, the objective response rate was 26% (95% CI, 12% to 45%). An additional seven patients (23%) had stable disease for > 4 months, bringing the overall rate of benefit to 48% (95% CI, 30% to 67%).

Seven of the eight patients who had an objective response had M1c disease, including four who had presence of liver metastases (Table 4). Five patients remain alive, with duration of survival > 35.3, > 34.7, > 28.2, > 25.8, and > 23 months. One of the patients still alive was not considered a responder and therefore is not listed in Tables 3 and 4.

Prior therapies received by patients showing clinical benefit are shown in Table 4, as well as whether the therapy was adjuvant or therapy for stage IV disease. The small study size precludes any meaningful assessment of the effect of prior therapy on response. However, an exploratory analysis was performed in an attempt to address (albeit in a qualitative manner) whether prior treatment affected outcome. Univariate Cox proportional hazards models were run to evaluate the relationship between prior therapies (prior biotherapy or prior chemotherapy or local radiation) and the duration of progression-free survival and overall survival (relative to the first day of treatment on

**Table 3.** Response to Chemobiotherapy, Time to Disease Progression, and Survival (N = 31)

Best Overall Response	No.	%	Time to Disease Progression (months)*	Duration of Survival (months)*
CR	4	13	10.5, 11.3, 27.5, and > 34.7	15.9, 24.4, 27.5, and > 34.7
PR	4	13	5.2, 6.1, 12.1, and 20.0	11.6, 14.8, > 28.2, and 30.8
SD	7	23	4.9, 5.1, 5.2, 6.9, 9.1, 14.3, and > 25.8	6.6, 7.8, 9.1, 13.1, 14.3, > 25.8, and > 35.3
Progressive disease	16	52		
Response rate (CR/PR)		26%		
95% CI		12% to 45%		
Response rate (CR/PR/SD)		48%		
95% CI		30% to 67%		

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.  
\*From day 1 of chemobiotherapy.

this protocol). Although neither variable was statistically significantly associated with the duration of progression-free survival and overall survival (smallest *P* value among models = .43), the data from this study suggest an increased risk of earlier progression and death for patients who received prior biotherapy and lower risks for patients who received either chemotherapy or local radiation before the study. Neither of these analyses accounts for the patient's disease stage at the time of study enrollment, nor any other patient- or disease-related variables that may be related to one or both of these outcomes.

Twenty-nine patients (94%) experienced disease progression (Table 5). The median duration of progression-free survival was 4.9 months (95% CI, 2.8 to 6.9 months; Fig 1). The overall progression-free rate was 29% at 1 year and 10% at 2 years. Twenty-six patients (84%) died (Table 5). The median duration of survival was 13.1

months (95% CI, 7.8 to 18.3 months; Fig 1) for all patients and 25.9 months for patients experiencing an objective response. The overall survival rate was 52% at 1 year and 25% at 2 years.

Two patients (6%) presently have no evidence of disease (NED) 34.7 and 25.8 months after the start of chemobiotherapy. Both of these patients had brain metastases treated before study entry. One patient, SF09, had a history of a primary melanoma, lymph node metastasis, and in transit metastasis treated with surgery. In July 2001, she was found to have three brain metastases, which were treated with stereotactic radiosurgery and whole-brain radiation. In December 2001, magnetic resonance imaging of the brain showed control of the brain lesions, but a computed tomography scan showed new metastases to the liver and lung. She was treated with six cycles of chemobiotherapy with a CR. She received

**Table 4.** Characteristics of Patients With Response

Patient No.	Age (years)	Sites of Metastases*	Prior Therapy	Stage	Current Status	Time to Disease Progression (months)†	Duration of Survival (months)†
<b>Complete response</b>							
JW01	85	Lymph node, liver, bone, spleen	None	M1c	Died	27.5	27.5
SF02	47	Ovary	GM-CSF‡, RT‡	M1c	Died	10.5	15.9
SF09	58	Lung, liver, (brain)	SR§	M1c	NED	>34.7	>34.7
SF14	55	SQ, lymph node, intra-abdominal mass	S§	M1c	Died	11.3	24.4
<b>Partial response</b>							
SF01	69	SQ, lymph node	INF‡, S§	M1a	Died	12.1	30.8
SF05	53	Liver	GM-CSF‡, RA§, RT‡ S§	M1c	Died	5.2	11.6
SF13	48	Lung, liver, bone	None	M1c	Died	6.1	14.8
SF15	51	Pancreas, lymph node	GM-CSF‡	M1c	AWD	20.0	> 28.2
<b>Stable disease</b>							
JW02	72	Lung, liver	None	M1c	Died	14.3	14.3
JW07	36	(Brain), (lung), lymph node	None	M1c	NED	> 25.8	> 25.8
SF04	53	Lymph node, lung, liver, spleen	None	M1c	Died	6.9	9.1
SF06	75	SQ, lung	Vaccine	M1b	Died	9.1	13.1
SF08	49	Lung	None	M1b	AWD	5.1	> 35.3
SF20	56	Lymph node, lung	GM-CSF	M1b	Died	4.9	6.6
SF21	58	SQ, lymph node, lung, bowel, spleen	None	M1c	Died	5.2	7.8

Abbreviations: GM-CSF, granulocyte macrophage colony-stimulating factor; RT, radiation therapy; SR, stereotactic radiotherapy; NED, no evidence of disease; S, surgery for stage IV disease; INF, interferon; SQ, subcutaneous; RA, radiofrequency ablation; AWD, alive with disease.

\*At start of chemobiotherapy. Items in parentheses were treated previously.

†From day 1 of chemobiotherapy.

‡Adjuvant therapy.

§Therapy for metastatic disease.

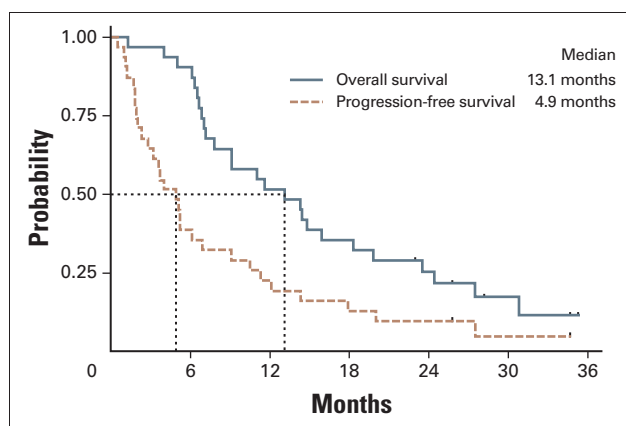
||Received maintenance therapy off protocol after achieving maximum benefit with low-dose chemobiotherapy.

**Table 5.** Summary of Progression-Free and Overall Survival (n = 31)

No. with progression	29
No. of deaths	26
Duration of progression-free survival (months)*	
Median	4.9
95% CI of the median	2.8 to 6.9
Range	0.5 to > 34.7
Overall progression-free rate at 12 monthst	
95% CI	10% to 38%
Overall progression-free rate at 24 monthst	
95% CI	2% to 23%
Duration of overall survival (months)*	
Median	13.1
95% CI of the median	7.8 to 18.3
Range	1.3 to > 35.3
Overall survival rate at 12 monthst	
95% CI	33% to 67%
Overall survival rate at 24 monthst	
95% CI	12% to 41%

\*The duration of progression-free and overall survival was calculated as the time elapsed between the first day of chemobiotherapy and progression and death (from any cause), respectively.  
 †Estimated using the Kaplan-Meier method. 95% CI calculated using Greenwood's formula for the SE.

one cycle of maintenance therapy but did not tolerate it well and has received no further therapy. She still exhibits NED and continues to work full time 34.7 months after study entry. The other patient, JW07, had a history of a primary melanoma. In March 2002, she was found to have a brain metastasis, left lower lung metastasis, and left hilar lymph node metastasis. She underwent a left lower lobe wedge resection, and the CNS lesion was subsequently treated with stereotactic radiosurgery. She was treated with four cycles of chemobiotherapy, during which time she had stable disease. She began receiving maintenance biotherapy and experienced a CR after the third cycle of treatment. She was treated with the maintenance regimen for 18 months and has NED 25.8 months after the start of biochemotherapy. She continues to work full time. Both patients are being followed with observation only.



**Fig 1.** Progression-free and overall survival for patients receiving chemobiotherapy.

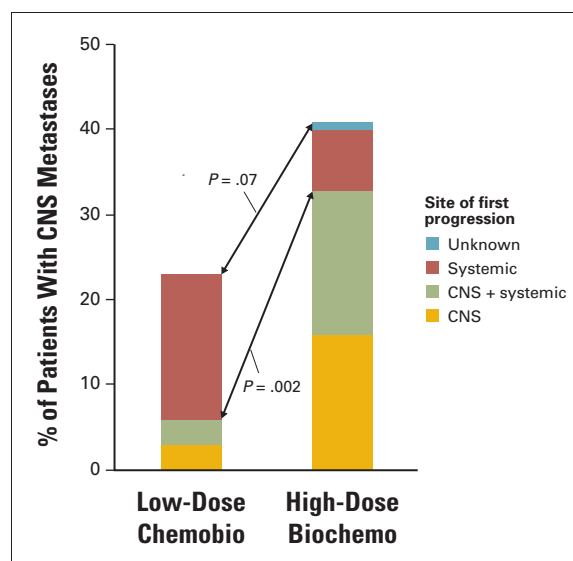
### CNS Metastases

All patients were assessable for development of new or progressive brain metastases as the first site of metastasis with or without systemic progression. Two patients (6%) developed brain metastases as the first site of disease progression, whereas development of brain metastases as the first site of disease progression occurred in 54 (33%) of the 163 patients on the high-dose inpatient regimen ( $P = .002$ , Fig 2). Furthermore, the two patients treated with the low-dose chemobiotherapy regimen described herein who had brain metastases previously treated with stereotactic radiotherapy before study entry are still alive and never developed progressive brain lesions.

One patient of the 31 participating in the study developed progression elsewhere and did not develop CNS metastases at that time, but was then lost to follow-up. It is unknown whether that patient ever developed CNS metastases and is therefore assessment for subsequent development of CNS metastases is not possible. Of the 30 patients who were assessable, seven (23%) developed CNS metastases after being treated with the low-dose outpatient chemobiotherapy regimen as compared with 68 of 163 patients (42%) treated with the high-dose inpatient DTIC-based biochemotherapy regimen ( $P = .07$ ; Fig 2).

### Toxicity

The treatment was generally well tolerated. Initially, patients were hospitalized for 1 day when they started receiving therapy with rIL-2. However, because rIL-2 was well tolerated, the requirement for hospitalization was dropped. Otherwise, the treatment was conducted entirely on an outpatient basis.



**Fig 2.** Percentage of patients developing CNS metastases while receiving low-dose chemobiotherapy (chemobio) using temozolomide and high-dose inpatient biochemotherapy (biochemo) protocol using dacarbazine.

Adverse events were noted in 78% of all treatment cycles (Table 6). These events were generally mild (grade 1 or 2) and easily managed. Grade 4 toxicity was noted in 3% of the cycles, including hematologic toxicity (thrombocytopenia) in two cycles (thought to be caused by temozolomide) and psychosis in one cycle (thought to be possibly related to the biologic therapies) that required hospitalization and discontinuation of treatment, even though the disease was responding to therapy.

The most common adverse events were flu-like symptoms (72% of cycles). These events were mostly grade 1 and 2 and included fatigue, chills/rigors, and fever. GI symptoms were also common, were usually grade 1 and 2, and included nausea, constipation, and anorexia. Other toxicities were seen less frequently and included skin manifestations in 20% of the cycles (injection site reaction, dry skin, or erythema), and neurologic toxicity in 13% of cycles (mood alteration, headache).

## DISCUSSION

The majority of the patients with metastatic melanoma included in this study had characteristics indicating a poor prognosis and predicting a short duration of survival in-

cluding M1c disease (90%), multiple sites of metastases (77%), and male sex (74%). Nonetheless, the results of this study suggest that this chemobiotherapy combination is clinically effective in these patients. We observed an objective response rate of 26% including 13% CR, a median survival of 13 months, and long-term survival (more than 2 years) in 25% of patients. There also appeared to be benefit in terms of delay or prevention of the development of brain metastases. Two of the patients (6%) developed brain metastases as the first site of disease progression and only seven (23%) developed CNS progression after chemobiotherapy. Five patients (16%) remain alive, two of whom (6%) have NED. This success rate was achieved with a therapy that was a low-dose outpatient regimen allowing home dosing. Moreover most of the toxicity was of mild to moderate severity, easily controlled in an outpatient setting, and not very disruptive to the patient's lifestyle.

In an analysis of prognostic factors in 1,158 patients with stage IV metastatic melanoma, it was found that the most significant differences were noted when visceral versus nonvisceral sites were compared.<sup>7</sup> This analysis formed the basis for the M classification in the current staging system of the American Joint Commission on Cancer (AJCC).<sup>8</sup> Many earlier reports also identified visceral metastases as an important indicator of poor prognosis.<sup>9,10</sup> The analysis that formed the basis for the current AJCC staging system did not incorporate information regarding the number of metastatic sites, so this was not included in the staging.<sup>7</sup> However, a number of other studies have determined that the number of metastatic sites is, indeed, an important prognostic indicator.<sup>9-11</sup>

The incidence of the development of CNS metastasis in this study was significantly different from that reported by O'Day et al (unpublished data) in terms of CNS as the first site of disease progression, either alone or in combination with systemic progression, and approached significance in terms of incidence of CNS metastases during or following therapy. In a retrospective analysis of patients with metastatic melanoma responding to DTIC- or temozolomide-based chemotherapy (n = 41), Paul et al<sup>12</sup> also found a statistically significant decrease in the development of CNS relapse in the patients receiving the regimen containing temozolomide. The Hellenic Cooperative Oncology Group conducted a study of temozolomide in combination with docetaxel in patients with advanced melanoma (n = 62) and reported that of 52 patients who did not have brain involvement at presentation, only four (8%) developed brain metastases at a median follow-up of 14 months.<sup>13</sup> In a pilot trial of concurrent biochemotherapy in which temozolomide was substituted for DTIC used in an earlier combination regimen, Atkins et al<sup>14</sup> found that initial CNS progression was significantly less frequent in the temozolomide-based

**Table 6.** Summary of Common Toxicities (number of cycles = 112)

Toxicity	All Grades	Grade*			
		1	2	3	4
All	78	47	55	10	3
Constitutional	72	29	42	2	0
Fatigue	54	20	33	1	0
Chills/rigors	29	12	16	2	0
Fever	21	4	14	2	0
Myalgia	6	4	3	0	0
Arthralgia	2	1	1	0	0
Sweats	1	0	1	0	0
Gastrointestinal	57	26	25	6	0
Nausea	20	5	11	4	0
Constipation	18	9	9	0	0
Anorexia	11	5	5	0	0
Vomiting	9	4	3	2	0
Dehydration	6	1	2	4	0
Diarrhea	5	2	4	0	0
Abdominal pain	3	2	1	0	0
Dyspepsia	1	1	0	0	0
Skin	20	12	8	0	0
Injection-site reaction	10	4	6	0	0
Dry skin	8	5	3	0	0
Erythema	6	4	2	0	0
Hematologic	13	4	4	4	2
Anemia	6	4	2	0	0
Neutropenia	4	0	1	4	0
Thrombocytopenia	4	0	2	0	2
Neurologic	13	3	9	1	1
Mood alteration	7	0	6	0	0
Headache	4	2	2	1	0
Psychosis	2	0	1	0	1
Dizzy	1	1	0	0	0
Respiratory	5	4	2	0	0
Cardiac arrhythmia	1	0	0	1	0
Other	2	0	2	0	0
Renal failure	2	0	2	0	0

\*According to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

regimen than in the DTIC-based biochemotherapy regimen (two of 22 v 12 of 19;  $P = .001$ ), but this analysis was limited to patients responding to biochemotherapy. When all patients who entered the temozolomide-based regimen were considered, the incidence of CNS progression was 67%.

The inclusion of temozolomide in the regimen described herein, rather than DTIC as used in other regimens, may account for this difference in outcome, because temozolomide crosses the blood-brain barrier,<sup>15,16</sup> whereas DTIC does not. Temozolomide is approved for the treatment of anaplastic astrocytoma and glioblastoma and has been reported to have activity in the treatment of brain metastases from malignant melanoma.<sup>17</sup>

Given the dismal outcome with previous therapeutic approaches, especially the US Food and Drug Administration–approved monotherapies DTIC<sup>18–20</sup> and rIL-2,<sup>21–23</sup> there has been enthusiasm for using chemotherapy and chemobiotherapy combinations. In many uncontrolled trials, of complex combinations of chemotherapy with and without cytokines, results were consistent with improved response rates and, possibly, survival. Results of randomized trials, however, showed that combination chemotherapy is no better than therapy with single-agent DTIC.<sup>19</sup> One randomized, single-institutional trial showed an improved objective response rate, time to progression, and a trend towards increased survival among patients randomly assigned to sequential biochemotherapy compared with chemotherapy alone.<sup>24</sup> However, randomized trials reported at the 2003 Annual Meeting of the American Society of Clinical Oncology (ASCO; Chicago, IL, May 31–June 3, 2003) indicated that chemobiotherapy is no better than combination chemotherapy.<sup>25–27</sup> This led L.M. Schuchter, in her 2003 ASCO lecture, to conclude that it's time to “wipe the slate clean and start over.”<sup>28</sup>

The high-dose biochemotherapy regimens require hospitalization and are disruptive of lifestyle in patients in whom life expectancy may be limited. Some studies have shown promising results in the outpatient setting, such as the temozolomide-thalidomide combination.<sup>29–31</sup> However, a trial of temozolomide and thalidomide in patients with melanoma metastatic to the brain was recently closed to accrual because of thrombotic events, presumably associated with thalidomide. Studies of outpatient regimens using lower doses of biologics in combination with chemotherapy have also appeared promising.<sup>32,33</sup> The study results described in this manuscript indicate that this low-dose chemobiotherapy regimen has activity, even in patients with M1c disease, and can be administered on an outpatient basis with manageable toxicity.

Three phase III trials of new agents for therapy of stage IV melanoma have been concluded in 2004 with disappointing negative results. These include a randomized trial of high-dose Revlimid (lenalidomide; Celgene

Corp, Summit, NJ) versus low-dose Revlimid in patients who had experienced treatment failure with first-line chemotherapy for metastatic melanoma.<sup>34</sup> A similar trial in Europe comparing high-dose Revlimid versus placebo in the same patient population also failed to show clinical benefit of Revlimid therapy.<sup>34</sup> A trial in melanoma patients with hepatic metastases of Maxamine (histamine dihydrochloride; Maxim Pharmaceuticals, San Diego, CA) with low-dose rIL-2 versus low-dose rIL-2 alone failed to show benefit of the combination therapy.<sup>35</sup> Finally, a trial of Genasense (oblimersen sodium, Genta Inc, Berkeley Heights, NJ), an inhibitor of BCL2, administered with DTIC compared with DTIC alone failed to show benefit of the combination.<sup>36</sup>

O'Day et al<sup>6</sup> have reported a maintenance biotherapy regimen that offers the potential to extend the clinical benefit in patients responding to the high-dose inpatient biochemotherapy regimen. This regimen includes subcutaneous rIL-2 and GM-CSF with monthly decrescendo intravenous rIL-2. It is noteworthy that three patients who received chemobiotherapy on this protocol subsequently received the maintenance regimen off protocol. The role of maintenance therapy should be considered in future studies.

There is no question that more-effective and less-toxic therapies for metastatic melanoma are desperately needed. The US Food and Drug Administration–approved therapy with single-agent chemotherapy, DTIC, has limited activity in patients with visceral metastasis. The alternative US Food and Drug Administration–approved therapy with high-dose rIL-2 requires inpatient administration, is associated with significant toxicity, and is most effective in patients with M1a disease. We strongly advocate recommendation to patients with metastatic melanoma that they participate in clinical trials that offer the potential for greater efficacy and less toxicity. However, for patients who decline the US Food and Drug Administration–approved therapies, and who are not candidates for or do not choose to participate in clinical trials, the regimen described herein has potential for clinical benefit (including the possibility of causing disease regression, benefiting progression-free and overall survival, and preventing or delaying the development of brain metastases) with limited toxicity in a regimen that permits home dosing. A randomized trial would be required to determine whether this combination provides greater efficacy and less toxicity than the currently approved therapies.

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### Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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