A Phase II Pilot Trial of Concurrent Biochemotherapy with Cisplatin, Vinblastine, Dacarbazine, Interleukin 2, and Interferon α-2B in Patients with Metastatic Melanoma[1]

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ABSTRACT

In an effort to develop a biochemotherapy regimen for metastatic melanoma suitable for testing in a cooperative group setting, we modified the concurrent biochemotherapy regimen of S. S. Legha *et al.* (J. Clin. Oncol., *16:* 1752–1759, 1998) by providing enhanced supportive care and developing a strict, conservative approach to the management of treatment-related toxicities. Patients received cisplatin, vinblastine, and dacarbazine (CVD: cisplatin (20 mg/m^2) and vinblastine (1.2 mg/m^2) on days 1–4, dacarbazine (800 mg/m^2) on day 1 only) concurrently with interleukin 2 (9 MIU/m^2/day) by continuous i.v. infusion on days 1–4 and IFN-α (5 MU/m^2/day) on days 1–5, 8, 10, and 12. Prophylactic antibiotics and a maximum of four cycles were administered. Routine granulocyte colony-stimulating factor and aggressive antiemetics were initiated after patients 7 and 14, respectively. Forty-four patients were enrolled in this study. No patients had received prior chemotherapy or interleukin 2; however, 23 (53%) had received prior IFN-α, mostly in the adjuvant setting. A total of 131 treatment cycles was administered. Significant toxicities requiring dose modification included: hypotension requiring pressors (15 episodes in 11 patients), grades 3/4 vomiting (12 episodes in 15 cycles; 5 episodes in 12 patients (6 episodes in 9 cycles after initiation of the modified antiemetic regimen), transient renal insufficiency (5 episodes in 5 patients), grade 4 thrombocytopenia (24 episodes, 1 associated with bleeding), neutropenia with or without fever (15 instances, only 11 in 112 cycles after routine use of granulocyte colony-stimulating factor), and catheter-related bacteremia (2 patients). Five (16%) of 30 patients who were treated after the last protocol modification experienced what we defined as unacceptable toxicity for a cooperative group setting. Responses were seen in 19 of 40 evaluable patients (relative risk, 48%) with 8 complete responses (20%). The median response duration was 7 months (range, 1–17+ months) with one currently ongoing. The central nervous system was the initial site of relapse in 11 responding patients. The median survival duration was 11 months (range, 2–31 months). This modified, concurrent biochemotherapy regimen is active and tolerable for use in a cooperative group setting. Central nervous system relapse, however, remains a concern for responders. This regimen is being compared with CVD in a Phase III Intergroup Trial (Eastern Cooperative Oncology Group/Southwest Oncology Group 3695).

INTRODUCTION

Historically, metastatic melanoma has been highly resistant to treatment. Single-agent chemotherapy regimens have produced response rates of 10–20%, with median response durations of only 4–5 months (1). DTIC[3] remains the most active single agent, with a response rate of approximately 20%, but the majority of DTIC-induced responses are partial and transient (2, 3). Combination chemotherapy regimens have produced higher response rates and apparent prolongations of median survival in some single-institution Phase II trials, but large-scale Phase III trials have failed to show significant benefits relative to DTIC alone (4–8).

Immunotherapy, specifically IL-2 and/or IFN-α, has also shown activity in metastatic melanoma (9, 10). High-dose bolus IL-2 alone has produced responses in 15–20% of patients, with 5–10% of patients achieving durable complete remissions (11). Similar response rates have been seen with single-agent IFN-α, but the quality and durability of these responses have, in gen-

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[3] The abbreviations used are: DTIC, dacarbazine; IL, interleukin; MDAAC, M. D. Anderson Cancer Center; ECOG, Eastern Cooperative Oncology Group; CT, computed tomography; CNS, central nervous system; SBP, systolic blood pressure; CVD, cisplatin, vinblastine, and DTIC; CR, complete response; PR, partial response; FEV1, forced expiratory volume in 1 s.

eral, been inferior to those reported with high-dose bolus IL-2 (12).

In an attempt to improve the response rate of patients treated with immunotherapy and the durability of response seen with combination chemotherapy, several investigators have combined cytotoxic chemotherapy with IL-2-based immunotherapy for the treatment of patients with metastatic melanoma. Composite results in nearly 400 patients who received cisplatin and IL-2-based biochemotherapy combinations have revealed a response rate of approximately 50%, with 10% of patients achieving a durable CR (13–17). These results have suggested a potential advantage of biochemotherapy over chemotherapy alone; however, they were achieved in single-institution, Phase II trials and have yet to be reproduced in a randomized Phase III trial of biochemotherapy *versus* chemotherapy. Unfortunately, most of the regimens used in these studies were too toxic and complicated to be evaluated by cooperative groups unaccustomed to high-dose IL-2-based regimens.

The concurrent biochemotherapy regimen developed at the MDACC was seen as an exception to these more toxic approaches (17). In this regimen, CVD is administered concurrently with IFN-α-2a and continuous infusion IL-2 over a 5-day period. This combination produced responses in 34 (11 complete, 23 partial) of 53 patients (response rate, 64%). Five patients (9%) remained disease free at >4 years. Although significant side effects were still observed, including neutropenic fever (64%), bacteremia (49%), and hypotension (39%), we believed that by providing enhanced supportive care and developing a strict, conservative approach to the management of hypotension and other toxicities, these side effects could be kept to a tolerable level. We now report the results of a pilot Phase II trial of this modified, concurrent biochemotherapy regimen in patients with metastatic melanoma.

PATIENTS AND METHODS

Patient Selection. All of the patients who were entered into this study had histologically confirmed, bidimensionally measurable, and clearly progressive metastatic melanoma. Eligible patients had an ECOG performance status of 0 or 1 and adequate organ function, as defined by WBC count >4,000/μl, platelet count >100,000/μl, serum bilirubin <1.5 mg/dl, serum creatinine <1.5 mg/dl, or calculated creatinine clearance >75 ml/min. Patients were required to have a FEV1 of >2.0 liters or ≥75% of predicted for height and age, and no history of congestive heart failure, serious cardiac arrhythmias, angina, or prior myocardial infarction. Patients who were >40 years of age or who had a history of cardiac disease were required to have a normal cardiac stress test. Screening tests for hepatitis B surface antigen and HIV antibody were required to be negative. Patients with active brain metastases on head CT scan, medical conditions requiring systemic corticosteroids, organ allografts, contraindications to the use of pressor agents, active infections requiring antibiotic therapy, a history of second malignancy other than nonmelanoma skin cancer, carcinoma *in situ*, or stage I carcinoma of the cervix were excluded. Patients who had received prior chemotherapy or IL-2 therapy were excluded. Prior immunotherapy with agents other than IL-2 in the adjuvant or metastatic setting was allowed, but this had to be completed ≥4 weeks before entry to the protocol. The protocol was approved by the Human Investigational Review Boards at both New England Medical Center and Beth Israel Deaconess Medical Center. Voluntary written informed consent was obtained from every patient.

Table 1 Modified concurrent biochemotherapy regimen

DTIC, 800 mg/m^2, day 1
CDDP,[a] 20 mg/m^2/day, days 1–4
Vinblastine, 1.2 mg/m^2/day, days 1–4
IFN-α-2b (Schering), 5 × 10^6 units/m^2 s.c., days 1–5, 8, 10, 12
IL-2 (Chiron), 9 × 10^6 IU/m^2/day by CIV for 4 days
G-CSF, 5 μg/kg s.c. qd days 7–16[b]
Zofran, 32 mg i.v. qd, Ativan 1 mg p.o./i.v. every 6 h[c]
Cycle every 21 days; assess response on day 42; maximum of 4 cycles

[a] CDDP, cisplatin; G-CSF, granulocyte colony-stimulating factor; qd, every day; CIV, continuous i.v.
[b] Routine after patient 7.
[c] Routine after patient 14.

Treatment Plan. The dose and schedule of this modified, concurrent biochemotherapy regimen are described in Table 1. Patients were admitted to the hospital for the first 6 days of each treatment cycle and were treated with CVD in combination with IL-2 (Proleukin, Chiron, Emeryville, CA) and IFN (Intron A, Schering Plow, Kenilworth, NJ). Therapy was administered on a regular oncology ward without any specialized patient monitoring. Patients were required to discontinue any antihypertensive therapy 24 h before beginning each treatment cycle. Before each course of therapy, patients underwent placement of a central venous catheter, which was then removed at the end of the first week of each cycle. Patients received ciprofloxacin 250 mg or Keflex 250 mg p.o. twice per day from day 1 to day 14 in an effort to prevent catheter-related infection. The administration of granulocyte colony-stimulating factor (5 μg/kg/day) on days 7 through 16 was made routine after patient number 7 and an aggressive approach to antiemetic therapy (ondansteron 32 mg i.v. every day, Ativan 1 mg i.v./p.o. every 6 h) was instituted after patient number 14. Acetaminophen (650 mg every 4 h) to was given to reduce febrile reactions, ranitidine (150 mg) p.o. every 12 h was given to prevent gastrointestinal bleeding; hydroxyzine hydrochloride (25–50 mg p.o. every 6 h) or diphenhydramine (25 mg p.o. every 6 h) was given for pruritis, and meperidine (25–50 mg i.v. every 3 h) for chills and rigors. Antidiarrheal agents and anxiolytics were given as needed.

Modifications to MDACC Concurrent Biochemotherapy Protocol. Modifications to the concurrent biochemotherapy protocol developed at the MDACC are depicted in Table 2. These changes included the use of prophylactic antibiotics (ciprofloxacin or Keflex) for days 1–14 and the removal of central lines after each inpatient cycle. The dose of vinblastine was reduced to 4.8 mg/m^2 per cycle. Granulocyte colony-stimulating factor (5 μg/kg/day) and antiemetic therapy (ondansteron 32 mg i.v. every day, Ativan 1 mg i.v./p.o. every 6 h) was administered as described above. A maximum of four rather than six treatment cycles was given. Strict, conservative, and explicit dose modification criteria were developed for the man-

Table 2 Modifications to the MDACC concurrent biochemotherapy regimen

Prophylactic antibiotics
Replace central lines each cycle (days 5–6)
Reduce vinblastine to 4.8 mg/m^2 per cycle.
G-CSF (days 7–16)
Aggressive antiemetics; delayed discharge and/or outpatient i.v. hydration if needed
Strict, conservative, and explicit dose modification criteria for: Hypotension Renal insufficiency Hematological toxicity CNS toxicity
Maximum of four cycles

agement of hypotension, renal insufficiency, hematological toxicity, and CNS toxicity.

Dose Modification Criteria. In general, patients experiencing grade 3 toxicity as described in the National Cancer Institute Common Toxicity Criteria while receiving therapy (days 1–5) had treatment (CVD, IL-2, and IFN) withheld until toxicity returned to grade 2 or less. Therapy was then restarted at full dose of chemotherapy and a 50% dose reduction of both IL-2 and IFN. If a portion of an IL-2 infusion was withheld or a dose of IFN was not given on schedule, it was not readministered. All of the dose reductions were permanent. If Grade 3 or 4 toxicity recurred despite dose reduction, no further IL-2 or IFN was administered in that cycle or subsequent cycles. If a grade 3 toxicity was encountered during week 2 of any cycle, remaining IFN injections were withheld for the rest of that cycle. Subsequent IFN was given at full dose. Exceptions to this general plan are detailed in the following sections.

Hypotension. Vital signs were monitored every 4 h for stable patients receiving IL-2. Patients experiencing a fall in SBP to <90 mm Hg received a bolus of 250 ml of normal saline fluid for >15 min. This was repeated once for recurrent hypotension. If the SBP did not increase to >90 mm Hg despite fluids, then IL-2 infusion was interrupted, and other therapy was withheld until the SBP increased to >90 mm Hg, at which time IL-2 and IFN were restarted at 50% of the baseline dose. If the SBP fell to <85 mm Hg (80 mm Hg for patients <40 years old with no history of cardiac disease or hypertension) regardless of response to fluid boluses, IL-2 infusion was interrupted, and IFN administration was withheld. Both agents were restarted at 50% of their original doses when the SBP increased to >90 mm Hg. If the SBP remained <85 mm Hg (80 mm Hg for patients <40 years old with no history of cardiac disease or hypertension), dopamine was started at 2 μg/kg/min and was increased up to a maximum of 6 μg/kg/min to keep SBP >90 mm Hg. IL-2 and IFN were restarted at 50% of their original doses when the SBP was >90 mm Hg, with no pressors. Patients who did not respond sufficiently to dopamine received Neo-Synephrine beginning at 0.2 μg/kg/min and increased as necessary to keep SBP at >90 mm Hg. Patients requiring both dopamine and Neo-Synephrine for blood pressure support did not receive additional IL-2 therapy during that cycle but received IFN at 50% dose reduction when the blood pressure recovered. Cisplatin and vinblastine also were withheld until the patient's SBP was >90 mm Hg without blood pressure support. If blood pressure failed to recover within 6 h of the scheduled time of cisplatin, vinblastine, and IFN administration, therapy was omitted for that day.

Nephrotoxicity. Patients had a serum creatinine checked before cisplatin administration on days 1 through 4. If serum creatinine was >1.6 mg/dl, cisplatin was withheld, and a 500-ml normal saline fluid bolus was administered. If the serum creatinine improved to ≤1.6 mg/dl within 4 h, scheduled cisplatin chemotherapy was administered. If creatinine remained at >1.6 mg/dl on that day or subsequent days, cisplatin was withheld. If creatinine remained >2.0 mg/dl despite fluid boluses, further cisplatin during that cycle was withheld. Missed doses of cisplatin were not replaced. Patients remained on vinblastine, IL-2, and IFN unless grade 3 nephrotoxicity (creatinine >3.0 mg/dl) developed. Subsequent cycles included full-dose cisplatin as long as the creatinine returned to ≤1.6 mg/dl.

Hematological Toxicity. Successive cycles of therapy were delayed if necessary until the WBC count and platelet count returned to the levels required to begin treatment. If the next cycle was delayed >2 weeks, the patient was removed from the study. Patients experiencing grade 4 hematological toxicity, grade 3 neutropenia with fever, or grade 3 thrombocytopenia with bleeding had a 25% dose reduction of vinblastine and DTIC on subsequent cycles. Patients with recurrent hematological toxicity, as described above, despite dose reduction had a second 25% dose reduction in subsequent cycles. Patients who, despite a 50% dose reduction in vinblastine and DTIC, developed hematological toxicity as described above were removed from the study. Patients experiencing grade 3 hematological toxicity during week 2 of IFN therapy (days 8, 10, or 12) had IFN withheld for the remainder of the week. IFN was then administered at full dose in subsequent cycles.

Neurotoxicity. Patients underwent a thorough neurological exam before each cycle of therapy. If a patient developed a peripheral neuropathy of grade 2 or higher, cisplatin administration was discontinued. Patients experiencing grade 2 neuropsychiatric or neurocortical toxicity during therapy had IL-2 and IFN withheld until toxicity returned to grade 1. IL-2 and IFN were then restarted at a 50% dose reduction for the remainder of therapy.

Response Criteria. Tumor measurements were obtained after the second cycle of therapy and compared with those obtained within 2 weeks of initiating treatment. Standard response criteria were used. CR was defined as the complete disappearance of all clinical and radiographic evidence of malignant disease for at least two determinations separated by a minimum of 4 weeks; PR was defined as a >50% decrease in the sum of the products of the perpendicular diameters of all of the measurable lesions for at least two determinations separated by a minimum of 4 weeks, with no new lesions or progression of existing lesions; minor response was defined as >25% but <50% decrease in the sums of the areas of all of the lesions on at least two determinations separated by a minimum of 4 weeks; progressive disease was defined as a >25% increase in the sum of the areas of all lesions or the appearance of any new lesion. Response durations were measured from the date of PR or CR and were updated through April 1, 1999.

Table 3 Patient characteristics

No. of patients	44
Treatment cycles	131
PS[a] (ECOG 0/1)	26/18
Gender (M/F)	25/19
Median age (range)	45 (19–71)
Sites of metastasis	
Lymph node/s.c.	8 (18%)
Visceral	36 (82%)
No. of metastatic sites	
1	10 (25%)
2	14 (35%)
>2	16 (40%)
Prior therapy	33 (75%)
XRT	8 (18%)
Systemic therapy	29 (66%)
IFN	23 (53%)
Other biological medication	8 (18%)
Chemo or IL-2	0
Ocular primary	2 (5%)

[a] PS, performance status; XRT, radiation therapy.

Table 4 Treatment characteristics

No. of cycles	Patients n = 44 (%)
1	5 (11)
2	12 (27)
3	2 (5)
4	25 (57)

Dose modifications	No. of patients (%)	No. of cycles (%)
IL-2/IFN[a]		
50% reduced	14 (32)	21 (16)
Discontinued	5 (11)	5 (4)
DTIC/VBL[b,c]		
25% reduced	13 (30)	18 (14)
50% reduced	6 (14)	6 (5)
CDDP[d]		
25% reduced	5 (11)	10 (8)
50% reduced	0 (0)	0 (0)

[a] IL-2/IFN: modified for hypotension, neurotoxicity (1), or cardiac (1).
[b] VBL, vinblastine.
[c] DTIC/VBL: modified for hematological toxicity.
[d] CDDP: modified for nausea/vomiting.

Statistical Methods. The initial study sample size (30) was chosen to determine with reasonable confidence (80%) whether this regimen was associated with <30% incidence of unacceptable toxicity (*i.e.*, hypotension requiring pressors or any toxicity requiring readmission) during the first two treatment cycles. If >7 patients developed significant toxicity during this period, the regimen would have been declared unacceptably toxic for use in a cooperative group setting and would have been modified or reevaluated. After 14 patients were treated, the protocol was modified in an attempt to reduce the incidence of hematological and gastrointestinal toxicity. The sample size was then increased to include 44 patients or 30 patients beyond the last protocol modification. Only the last 30 patients were analyzed for purposes of this safety end point.

Actuarial estimates of survival were calculated according to the method of Kaplan and Meier (18). The association of patient characteristics (*i.e.*, performance status, gender, prior therapy, number of sites of disease, and sites of metastasis) with treatment response was tested using Fisher's exact test. All of the *P* values reported are two-sided. All of the statistical analyses were performed using SAS version 6.12 software package. Data were updated and analyzed as of April 1, 1999.

RESULTS

Patient Characteristics. Between February 1996 and November 1997, 44 patients with metastatic melanoma were entered into this study. Characteristics of the patients enrolled in this study are displayed in Table 3. Of the 44 patients, 26 had an ECOG performance status of 0, and 18 had a performance status of 1; 25 patients were men and 19 were women, and the median age was 45 years (range, 19–71 years). Thirty-three patients (75%) had received therapy in addition to surgery before entering this protocol, including eight patients (18%) who had received local radiation therapy and 29 (66%) who had received systemic therapy. Twenty-three (53%) of 44 patients had received IFN in the adjuvant setting; however, no patient had received prior chemotherapy or IL-2 therapy. Sixteen (36%) of 44 patients had more than two sites of metastatic disease, and 18 (41%) patients had liver and/or bone metastases.

Treatment Characteristics. A total of 131 treatment cycles was administered during this trial. A summary of treatment administered and dose modifications is displayed in Table 4. Thirty-nine patients (89%) received at least two cycles of therapy, and 25 (57%) received more than two cycles of therapy. Common reasons for dose modification included hypotension (IL-2 and IFN), neutropenia and thrombocytopenia (DTIC and vinblastine), and nausea/vomiting (cisplatin).

Toxicity Data. Grade 1 and 2 toxicities including fever, chills, nausea, skin rashes, anemia, neutropenia, and thrombocytopenia were seen in most patients. The incidences of grade 3 or 4 toxicities seen in the trial as a whole are depicted in Table 5. The most common significant toxicities were myelosuppression and nausea/vomiting. Grade 4 neutropenia occurred in five (71%) of the first seven patients. After the protocol was amended to include the routine administration of G-CSF, 8 (22%) of 37 patients developed grade 4 neutropenia, and neutropenic fever developed in 1 (0.8%) of 118 subsequent cycles of therapy. Grade 3 or 4 nausea/vomiting occurred in 12 patients (27%) and during 15 (11%) treatment cycles. After the initiation of the modified antiemetic regimen, severe nausea/vomiting was seen in 5 patients (17%) and during 6 (6%) treatment cycles. Central venous catheter-related bacteremia was documented in 2 patients. Grade 4 thrombocytopenia occurred in 19 patients (43%) and during 24 (18%) cycles, but only one episode was associated with bleeding (tongue bleeding, which resolved with platelet transfusion).

Hypotension requiring vasopressor support occurred in 11 patients (25%) and during 15 treatment cycles (11%). Four patients developed a second episode of hypotension requiring vasopressor support while receiving 50% of the original IL-2 and IFN doses. No patient required dopamine for >24 h or

Table 5 Toxicity results

	Patients	Cycles
	$n = 44$ (%)	$n = 131$ (%)
Hypotension	11 (25)	15 (11)
Hematological toxicity		
Grade 4 neutropenia	13 (30)	15 (11)
Neutropenic fever	4 (9)	4 (3)
Infection	3 (7)	3 (2)
Grade 4 platelets	19 (43)	24 (18)
Bleeding	1 (2)	1 (1)
Renal insufficiency[a]	5 (11)	5 (4)
Nausea/Vomiting (grade 3 or 4), total	12 (27)	15 (11)
Neurological toxicity	2 (5)	2 (2)
Readmission, total	15 (34)	17 (13)

[a] Creatinine > 1.6 during medication; CDDP dose(s) omitted (five patients, seven doses).

Table 6 Toxicity results in last 30 patients

	Patients	Cycles
	$n = 30$ (%)	$n = 96$ (%)
Hypotension	9 (30)	12 (13)
Hematological toxicity		
Grade 4 neutropenia	5 (16)	5 (5)
Neutropenic fever	0 (0)	0 (0)
Infection	2 (6)	2 (2)
Grade 4 platelets	15 (50)	20 (21)
Bleeding	0 (0)	0 (0)
Renal insufficiency[a]	4 (13)	4 (4)
Nausea/Vomiting (Grade 3 or 4), total	5 (16)	6 (6)
Neurological toxicity	2 (6)	2 (2)
Readmission, total	7 (23)	8 (8)

[a] Creatinine > 1.6 during drug; CDDP dose(s) omitted (four patients, five doses).

required Neo-Synephrine for blood pressure support. Renal insufficiency (creatinine > 1.6 mg/dl during therapy) and neurological toxicities were both uncommon. No major cardiac, pulmonary, or hepatic toxicity was noted in any patient, and no patient required transfer to the intensive care unit during therapy. There were no treatment-associated deaths.

Fifteen patients (34%) required readmission to the hospital or a delay in discharge during 17 treatment cycles (13%). The majority of these readmissions or delays in discharge were for neutropenia and fever or dehydration secondary to nausea/vomiting. Toxicity observed in the last 30 patients is displayed in Table 6. After the routine use of G-CSF and the modified antiemetic regimen, 7 patients (23%) required readmission or a delay in discharge. This involved 8 (8%) treatment cycles.

Response Data. Of the 44 patients who received therapy, 40 patients were evaluable for response. Two patients refused further therapy or evaluation after exhibiting clinically apparent responses to the first cycle of treatment. These two patients and two patients with metastases from choroidal primary melanomas were excluded from the response analysis. Tumor responses were seen in 19 patients (48%) with a median duration of 7 months (range, 2–28+ months; Table 7). Eight patients (20%) had a CR to therapy and 11 patients (28%) had a PR. One response is ongoing at 28 months. The CNS was the initial site of relapse for 11 of the 19 responding patients, including 4 of 8 complete responders.

Predictors of Response. Response rates by various patient characteristics are listed in Table 8. The response rate to this biochemotherapy did not correlate with ECOG performance status ($P = 0.2$), gender ($P = 0.75$), prior therapy ($P = 0.7$), prior IFN therapy ($P = 1.0$), prior radiation therapy ($P = 1.0$), number of disease sites ($P = 0.4$), or presence of visceral metastasis ($P = 1.0$).

Survival Data. The median survival duration for the 42 patients (2 patients with ocular melanoma excluded) was 11 months (range, 2–31 months; Fig. 1).The median survival of patients who achieved a CR was 16.5 months (range, 6–31 months). Nineteen patients survived longer than 12 months. Six patients remain alive at a median of 21 months, one patient is disease-free, and five are alive with disease.

DISCUSSION

The concurrent biochemotherapy regimen developed at the MDACC resulted in impressive antitumor effects but significant side effects in a large portion of patients, including neutropenic fever (64%), bacteremia (49%), and hypotension (39%). For the 30 patients treated in this study after the last modification to the MDACC protocol, the most frequent side effects were limited to myelosuppression and nausea/vomiting. Neutropenic fever was not seen in this cohort, and infection was documented in two patients (6%). Hypotension occurred in 13% of treatment cycles and was invariably transient and not associated with clinical sequelae. Typical high-dose IL-2-associated toxicities, including renal insufficiency, neurotoxicity, and pulmonary or cardiac toxicity, were uncommon, occurring in <5% of treatment cycles (19–21). No patient required transfer to an intensive care unit, and there were no treatment-related deaths. By providing enhanced supportive care and requiring a strict, conservative approach to the management of hypotension and other toxicities, these side effects can be kept to a tolerable level. This will allow this modified, concurrent biochemotherapy regimen to be tested in a cooperative group setting.

This modified, concurrent biochemotherapy regimen seems to maintain antitumor activity. The objective response rate (CR + PR) of 48% and the CR rate of 20% are consistent with the results observed with other biochemotherapy regimens (13–17). Responses were seen in all of the disease sites and with equal frequency in patients who had received prior IFN therapy in the adjuvant setting. In contrast to other systemic treatments in melanoma, patient response did not correlate with patient performance status, gender, prior therapy, number of disease sites, or specific disease sites.

The durability of responses and the percentage of durable CRs was disappointingly low. The median response duration was 7 months, with only one patient long-term disease-free. This disappointing result was, in large part, attributable to a high frequency of CNS relapse. Of the 19 patients who responded to therapy, 11 relapsed initially in the CNS. Eight of these 11 patients relapsed within 8 months of their initial response. Similar, although less dramatic, problems with CNS relapse have been seen by other investigators in patients responding to

Table 7 Response characteristics results

n	Evaluated	CR	PR	Not evaluated[a]	CR + PR
44	40	8 (20%)	11 (28%)	4	19 (48%)

Response duration (median, 7 months)

CR	26+, 22, 15,[b] 8,[b] 7, 7,[b] 6,[b] 3[b]
PR	14,[b] 10, 8,[b] 7,[b] 4, 4, 3, 2,[b] 2,[b] 2, 2[b]

[a] Two patients were lost to follow-up and two with ocular primary tumor were excluded.

[b] CNS initial site of relapse in 11 responding patients.

Table 8 Response correlates

	Total no. of patients	No. of patients (CR + PR)	%
Performance status ($P = 0.2$)			
0	25	14	56
1	15	5	33
Gender ($P = 0.75$)			
Male	23	10	43
Female	17	9	53
Prior therapy			
Any prior therapy ($P = 0.7$)	32	16	50
No prior therapy	8	3	38
Prior interferon ($P = 1.0$)	23	11	48
No prior interferon	17	8	47
Prior radiation ($P = 1.0$)	7	3	42
No prior radiation	33	16	47
Sites of disease ($P = 0.4$)			
1	10	3	30
2	14	8	57
≥3	16	8	50
Sites of metastasis ($P = 1.0$)			
s.c./lymph node only	8	4	50
Visceral	32	15	47

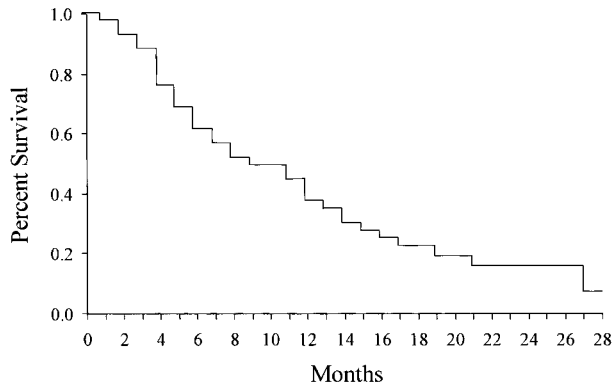

Fig. 1 Kaplan-Meier plot of overall survival for 42 patients. The median survival duration was 11 months.

IL-2-based therapy (15, 22). Because the agents in this concurrent biochemotherapy protocol do not penetrate into the CNS, these CNS relapses likely stem from progression of metastatic disease that was below the level of detection of the pretreatment head CT scan. Perhaps the general poor prognosis of this patient population (82% with visceral disease and 75% with more than one site of metastasis) contributed to this high frequency of CNS involvement before treatment.

As systemic therapy for metastatic disease improves, isolated CNS relapse is likely to become a more prevalent obstacle. Clearly, new approaches need to be developed for controlling or preventing CNS metastases. Temozolomide, an analogue of DTIC that is well absorbed p.o. and is able to penetrate into the CNS, and fotemustine, a chloroethyl nitrosourea that rapidly crosses the blood-brain barrier, are two agents that could be included in biochemotherapy regimens that may potentially reduce this problem (23, 24). Alternatively, prophylactic CNS radiation could be used after biochemotherapy in major responders to prevent CNS metastases from developing. Another alternative might be to consider biochemotherapy administration in the high-risk adjuvant setting in which the likelihood of CNS seeding may be lower.

Other factors may have contributed to the short response duration and limited durable CR rate in this population. One factor is the high frequency of prior IFN exposure in this cohort. This adjuvant therapy may have fostered the development of a population of metastatic cells that were resistant to the immunomodulatory component of the therapy, resulting in clinical progression shortly after treatment ceased. Another factor is the duration of therapy. The MDACC concurrent biochemotherapy regimen treated patients for six cycles. In this trial. treatment was limited to four cycles of therapy in an attempt to decrease the incidence of cumulative toxicity (*i.e.*, neurotoxicity, hematological toxicity, fatigue, and weight loss) that was seen in the MDACC trial (17). However, if an immunomodulatory mechanism is responsible for the improved response rates seen with biochemotherapy relative to chemotherapy alone, it is unlikely that two more cycles of therapy would be necessary to trigger it.

Despite impressive response rates in this study and other single-institution Phase II trials, there is currently no definitive evidence that biochemotherapy provides a clear advantage over chemotherapy alone in the treatment of metastatic melanoma. Recently, several randomized Phase III investigations of biochemotherapy have been initiated. The National Cancer Institute Surgery Branch has compared the combination of cisplatin, DTIC, and tamoxifen, plus high-dose IL-2 and IFN-α to cisplatin, DTIC, and tamoxifen alone (25). They reported that the response rate on the biochemotherapy arm (44%) was higher than the chemotherapy-alone arm (27%), but this improved antitumor activity did not translate into an improved CR rate, number of durable CRs, or overall survival. The European Organization for Research and Treatment of Cancer Melanoma Group has recently completed a randomized Phase III trial that compared biotherapy-alone (IL-2 and IFN) with biotherapy and cisplatin chemotherapy in metastatic melanoma (26). They concluded that both regimens were feasible in multicenter setting. Although the response rate (33 *versus* 18%; $P = 0.04$) and progression-free survival duration (92 *versus* 53 days; $P = 0.02$) were significantly higher for the combination arm, there was no difference in either overall survival or percentage of patients remaining progression-free. These data raise concerns about the true benefit of biochemotherapy and underscore the need to study this question in large, multicenter, randomized Phase III trials. The implementation of such a trial has been hampered by

the lack of a regimen suitable for testing in a cooperative group setting. The development of this modified concurrent biochemotherapy regimen has made it feasible to mount such a Phase III trial. This regimen is now being compared with CVD alone in a Phase III trial (E3695) within the ECOG and Southwest Oncology Group.

Depite the lack of a clear overall survival benefit in Phase III trials to date, all of the studies suggest that biochemotherapy can produce improved objective response rates, relative to chemotherapy or immunotherapy alone. These data suggest potential synergistic interactions between chemotherapy and immunotherapy components of these regimens. The proposed mechanisms of this potential synergy include cytokine enhancement of cisplatin-related DNA damage and cytotoxic chemotherapy-induced enhancement of melanoma antigen presentation, among others. Evidence supporting these various mechanisms are emerging from preclinical investigations and correlative laboratory studies conducted in conjunction with ongoing clinical trials (27–30). Understanding such mechanisms may not only lead to improved treatments for melanoma but also expand the therapeutic options for patients with other cisplatin- or IL-2-sensitive malignancies.

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