Prospective Randomized Trial of the Treatment of Patients With Metastatic Melanoma Using Chemotherapy With Cisplatin, Dacarbazine, and Tamoxifen Alone or in Combination With Interleukin-2 and Interferon Alfa-2b

By Steven A. Rosenberg, James C. Yang, Douglas J. Schwartzentruber, Patrick Hwu, Francesco M. Marincola, Suzanne L. Topalian, Claudia A. Seipp, Jan H. Einhorn, Donald E. White, and Seth M. Steinberg

Purpose: **The combination of chemotherapy with immunotherapeutic agents such as interleukin-2 and interferon alfa-2b has been reported to provide improved treatment results in patients with metastatic melanoma, compared with the use of chemotherapy alone. We have performed a prospective randomized trial in patients with metastatic melanoma, comparing treatment with chemotherapy to treatment with chemoimmunotherapy.**

Patients and Methods: **One hundred two patients with metastatic melanoma were prospectively randomized to receive chemotherapy composed of tamoxifen, cisplatin, and dacarbazine or this same chemotherapy followed by interferon alfa-2b and interleukin-2. Objective responses, survival, and toxicity in the two groups were evaluated at a median potential follow-up of 42 months.**

Results: **In 52 patients randomized to receive chemotherapy, there were 14 objective responses (27%), including four complete responses. In 50 patients randomized to receive chemoimmunotherapy, there were 22 objective responses (44%) (P_2 = .071), including three complete responses. In both treatment groups, the duration of partial responses was often short, and there was a trend toward a survival advantage for patients receiving chemotherapy alone (P_2 = .052; median survival of 15.8 months compared with 10.7 months). Treatment-related toxicities were greater in patients receiving chemoimmunotherapy.**

Conclusion: **With the treatment regimens used in this study, the addition of immunotherapy to combination chemotherapy increased toxicity but did not increase survival. The use of combination chemoimmunotherapy regimens is not recommended in the absence of well-designed, prospective, randomized protocols showing the benefit of this treatment strategy.**

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MULTIPLE APPROACHES have been used for the treatment of patients with metastatic melanoma. Single chemotherapeutic agents such as dacarbazine and cisplatin cause objective responses in 10% to 20% of patients, and combinations of these agents with nitrosoureas or vinca alkaloids have reported response rates of 30% to 40% (reviewed in[1,2]). The addition of tamoxifen to these chemotherapy regimens has been reported to increase response rates further.[3,4] The administration of high-dose bolus interleukin-2 (IL-2), recently approved by the United States Food and Drug Administration for the treatment of patients with metastatic melanoma, has reported response rates of 15% to 20%, as does treatment with single-agent interferon alfa-2b (reviewed in[5,6]). Recently, several reports have suggested that chemotherapeutic agents administered in combination with IL-2 and interferon alfa-2b can improve response rates to 55% to 60%, with complete response rates between 10% and 20%.[7-9] The toxicity associated with combining chemotherapy with IL-2 and interferon alfa-2b is substantial, and the benefit of this combination approach is based largely on phase II studies compared with historical controls.

We have performed a prospective randomized trial in patients with metastatic melanoma treated either with a chemotherapy regimen composed of cisplatin, dacarbazine, and tamoxifen or with this same chemotherapy plus the administration of intravenous (IV) high-dose bolus IL-2 and subcutaneous interferon alfa-2b. In this prospective randomized trial of 102 patients with a median potential follow-up of 42 months, there was no suggestion that the chemoimmunotherapy regimen that we have used is superior to chemotherapy alone. There was, however, a substantial increase in toxicity in patients treated on the chemoimmunotherapy arm.

PATIENTS AND METHODS

Patients

All patients had biopsy-confirmed metastatic melanoma and were treated in the Surgery Branch of the National Cancer Institute between March 15, 1993, and January 27, 1997. Patients with primary ocular or

From the Surgery Branch and Department of Biostatistics and Data Management Section, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD.

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Address reprint requests to Steven A. Rosenberg, MD, PhD, Surgery Branch, Division of Clinical Sciences, National Cancer Institute, 9000 Rockville Pike, Building 10, Room 2B42, Bethesda, MD 20892; email steven_rosenberg@nih.gov.

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mucosal melanoma were not included. All patients had measurable, clinically progressive disease and had received no other therapy for at least 1 month before entering onto this protocol. Patients were not eligible for this protocol if they had previously received chemotherapy with either cisplatin or dacarbazine or had previously received immunotherapy with either IL-2 or interferon alfa-2b. Patients were not eligible if they had evidence of CNS metastases or had major concomitant illnesses of the cardiovascular, respiratory, or renal systems that might preclude the administration of high-dose bolus IL-2. All patients older than 50 years underwent a stress electrocardiogram or a stress radionuclide thallium scan, and patients with evidence of ischemic heart disease or significant arrhythmias were excluded. At the time of entrance onto the study, patients had WBC counts greater than 3,000/mm^3, platelet counts greater than 100,000/mm^3, serum creatinine less than 1.7 mg/dL, and bilirubin less than 1.6 mg/dL and were seronegative for HIV antibody and hepatitis B antigen. All patients were assessed as of January 1, 1998, with a median potential follow-up of 42 months.

Before entry onto the protocol, all patients signed an informed consent approved by the investigational review board of the National Cancer Institute. Computed tomographic (CT) or magnetic resonance imaging scan of the brain, chest CT scan or full-lung tomogram, abdominal CT scan, and radionuclide bone scans were obtained before initiating treatment.

Treatment

All patients were prospectively randomized to receive treatment with either chemotherapy or chemoimmunotherapy. A schema of the chemoimmunotherapy regimen is presented in Table 1. Patients randomized to receive chemotherapy alone received this exact regimen but without interferon alfa-2b or IL-2. A treatment course consisted of two cycles, beginning on days 1 and 23 of a 2-month treatment course. All patients received an identical chemotherapy regimen, which consisted of tamoxifen starting on day 1 at 40 mg orally, followed by 10 mg orally bid on days 2 to 29. The first cycle of chemotherapy consisted of the administration on days 2, 3, and 4 and days 23, 24, and 25 of cisplatin 25 mg/m^2 IV over 30 minutes and dacarbazine 220 mg/m^2 IV over 1 hour. Patients randomized to receive chemoimmunotherapy received this identical chemotherapy regimen, followed, beginning on days 5 and 26, by 4 days of interferon alfa-2b at 6,000,000 U/m^2 subcutaneously and IL-2 at 720,000 IU/kg IV over 15 minutes every 8 hours to patient tolerance. IL-2 was administered until grade 3 toxicity was reached and could not be easily reversed by standard supportive measures. Thus, each treatment course consisted of 29 days of tamoxifen with two 3-day cycles of chemotherapy, followed, in those patients randomized to receive immunotherapy, by 4 days of treatment with interferon and IL-2.

Table 1. Treatment Schema

Cycle and Day	Treatment		
Cycle 1			
1			TAM
2	cDDP	DTIC	TAM
3	cDDP	DTIC	TAM
4	cDDP	DTIC	TAM
5	IFNα	IL-2	TAM
6	IFNα	IL-2	TAM
7	IFNα	IL-2	TAM
8	IFNα	IL-2	TAM
9-22			TAM
Cycle 2			
23	cDDP	DTIC	TAM
24	cDDP	DTIC	TAM
25	cDDP	DTIC	TAM
26	IFNα	IL-2	TAM
27	IFNα	IL-2	TAM
28	IFNα	IL-2	TAM
29	IFNα	IL-2	TAM
57	Evaluate clinical response; re-treat if tumor stable or regressing		

Abbreviations and dosage: cDDP, cisplatin, 25 mg/m^2 IV over 30 minutes; DTIC, dacarbazine, 220 mg/m^2 IV over 1 hour; IFNα, interferon alfa-2b, 6,000,000 U/m^2 subcutaneously; IL-2, interleukin-2, 720,000 IU/kg IV over 15 minutes every 8 hours; TAM, tamoxifen, 40 mg orally the night of day 1, then 10 mg orally bid.

Patients receiving cisplatin were vigorously prehydrated with the IV infusion of saline at 150 mL/hour, which continued during the administration of cisplatin and for 8 hours afterward. All patients receiving immunotherapy received concomitant medications, including acetaminophen (650 mg every 4 hours), indomethacin (50 mg every 8 hours), and ranitidine (150 mg every 12 hours) to prevent some of the side effects associated with IL-2 administration. All treatment was given to inpatients on a general surgical ward, although some patients were transferred to an intensive care unit for monitoring or for the administration of vasopressors if necessary.

Statistical Design

Randomization between the two study arms was performed by the central data management office. Patients were stratified according to site of disease: only subcutaneous or lymph node versus any visceral disease. This protocol was designed to accrue 67 patients in each of the two randomized arms in order to have 80% power to identify a 25% improvement in overall response rate, from 30% with chemotherapy alone, to 55% with chemoimmunotherapy, with alpha = .05 (two-tailed). Interim evaluations were planned, and if a difference in overall responses was significant at the alpha = .01 (two-tailed) level at any of the planned accrual interim evaluations, then accrual would stop. The protocol also stated that overall survival would be followed and compared between the two groups.

Evaluation of Response

All patients received at least two courses of treatment unless the rapid progression of disease or irreversible toxicity precluded the administration of a second course. At the end of each treatment course, patients received an evaluation of all known sites of disease. If patients showed evidence of stable or regressing disease, additional courses of treatment were administered. If, after two courses of treatment, patients exhibited evidence of progressive disease, no further therapy was administered as part of this protocol.

A response was considered complete if all measurable tumor disappeared for at least 1 month. A partial response was defined as a 50% or greater decrease of the sum of the product of the longest perpendicular diameters of all lesions lasting at least 1 month and without increase of any tumor or the appearance of any new tumor. Any patient not achieving at least a partial response was considered a nonresponder. All treated patients were evaluated for both toxicity and response. Comparisons between groups were assessed using the χ^2 test or Fisher's exact test. The probability of remaining in complete remission as a function of time as well as the probability of dying from disease were determined by the Kaplan-Meier method.[10] The statistical

significance of the difference between Kaplan-Meier curves was determined by the Mantel-Haenszel test.[11] All *P* values are two sided and denoted by P_2.

RESULTS

Patient and Treatment Characteristics

Between March 15, 1993, and January 27, 1997, a total of 102 patients were randomized, with 52 patients to receive chemotherapy and 50 patients to receive chemoimmunotherapy. The characteristics of these patients are listed in Table 2. Seventy-five percent of the patients were between the ages of 31 and 60 years, and all but one patient had an Eastern Cooperative Oncology Group performance status of 0 or 1. All patients had undergone prior surgery for the treatment of melanoma, and several patients had received prior chemotherapy or immunotherapy but not with any of the agents used in the current treatment protocol. Sex, age, performance status, sites of disease, and prior treatment were balanced between the two treatment arms; no factors differed significantly between the two arms. The treatment administered to patients is summarized in Table 3. Thirty-five percent of patients in the chemotherapy arm received one course of treatment, 33% received two courses, and 35% received three or four courses of treatment. Similarly, in the chemoimmunotherapy arm, 32% of patients received one course of treatment, 44% received two courses of treatment, and 24% received three or four courses of treatment. Few patients could tolerate the planned 12 doses of IL-2 per treatment cycle (Table 3), although 84% of patients received all of the planned interferon alfa-2b. Some patients developed limiting toxicity to cisplatin, and that agent was omitted from later cycles.

Table 2. Patient Characteristics

	Chemotherapy (n = 52)		Chemoimmunotherapy (n = 50)		Total (n = 102)	
	No.	%	No.	%	No.	%
Sex						
Male	30	58	33	66	63	62
Female	22	42	17	34	39	38
Age group, years						
11-20	2	4	0	0	2	2
21-30	4	8	4	8	8	8
31-40	13	25	16	32	29	28
41-50	14	27	15	30	29	28
51-60	12	23	13	26	25	25
61-70	7	13	2	4	9	9
Performance status						
0	47	90	38	76	85	83
1	5	10	11	22	16	16
2	0	0	1	2	1	1
Prior therapy						
Surgery	52	100	50	100	102	100
Chemotherapy	2	4	1	2	3	3
Radiotherapy	2	4	5	10	7	7
Immunotherapy	8	15	5	10	13	13
Any 2 or more	11	21	10	20	21	21
Any 3 or more	1	2	1	2	2	2
Site*						
Any visceral	33	62	35	70	68	67
Any subcutaneous	21	40	19	38	40	39
Any lymph node	20	38	23	46	43	42

*Sites total greater than 100% because patients have multiple sites of disease.

Table 3. Treatment Characteristics

	Chemotherapy (n = 52)		Chemoimmunotherapy (n = 50)	
	No.	%	No.	%
No. of courses				
1	18	35	16	32
2	16	33	22	44
3	12	21	11	22
4	6	11	1	2
Total	110	100	97	100
IL-2, no. of doses/course				
0	110	100	—	—
1-5	—	—	4	4
6-10	—	—	25	26
11-15	—	—	48	49
16-20	—	—	20	21
IL-2, total (IU $\times$ 10^{-3}/kg)/course				
0	110	100	—	—
1-3,600	—	—	4	4
3,601-7,200	—	—	25	26
7,201-14,400	—	—	68	70
IFN-α-2b, no. of doses/course				
0	110	100	1	1
1	—	—	1	1
4	—	—	12	12
5	—	—	1	1
6	—	—	1	1
8	—	—	81	84
Cisplatin, no. of doses/course				
0	—	—	3	3
1	—	—	3	3
3	8	7	8	8
4	—	—	9	9
5	—	—	1	1
6	102	93	73	75

Response to Therapy

Responses and response durations are presented in Tables 4 and 5. Of 52 patients randomized to receive chemotherapy alone, there were four complete responders and 10 partial responders, for a 27% objective response rate. Of the 50 patients randomized to receive chemoimmunotherapy, there were three complete responders and 19 partial responders, for a 44% objective response rate. Thus, there was a trend

Table 4. Response to Treatment

	Chemotherapy (n = 52)	Chemoimmuno-therapy (n = 50)
No. (%) of patients		
Complete response	4 (8)	3 (6)
Partial response	10 (19)	19 (38)
Duration, months		
Complete response	48+, 46+, 38, 9	46+, 13, 10
Partial response	50+, 37+, 13, 11, 11, 10, 10, 9, 6, 5	30+, 28, 11, 10, 9, 7, 7, 6, 6, 5, 5, 5, 5, 4, 4, 4, 4, 4

toward an increase in overall response in patients receiving chemoimmunotherapy ($P_2 = .071$, by χ^2 test). The 95% confidence interval for the difference in overall response rates extended from 1.2% favoring chemotherapy to 35.4% favoring chemoimmunotherapy.

The survival of patients is shown in Fig 1. There was a trend toward a survival advantage for patients receiving chemotherapy alone, compared with those receiving chemoimmunotherapy ($P_2 = .052$; not corrected for the yearly analyses of data during the trial). The median survival of patients receiving chemotherapy was 15.8 months, compared with 10.7 months for patients receiving chemoimmunotherapy. As an illustration of the magnitude of the difference at 2 years, the survival in the chemotherapy and chemoimmunotherapy patients was 31% and 14%, respectively, with a 95% confidence interval on the difference in survival at 2 years extending from 1% favoring chemoimmunotherapy to 33.5% favoring chemotherapy.

This protocol was originally designed to accrue 67 patients in each of the two randomized arms, as stated previously. Interim analyses were performed on an annual basis by the National Cancer Institute Data Safety and Monitoring Board, and analyses did not indicate the need to stop accrual. However, although response was the primary end point, because it became apparent that patients receiving chemoimmunotherapy were not surviving as long as those receiving chemotherapy, an additional evaluation at a convenient time point, 2 years, was selected to indicate the magnitude of the difference in survival between the arms, in addition to presentation of the overall survival curves. Because of the increased toxicity in the chemoimmunotherapy arm and because there was a 98% chance that chemotherapy was at least slightly superior to chemoimmunotherapy with respect to 2-year survival probability, accrual was ended early. It thus seems that the treatment with this chemotherapy regimen is at least as effective, if not more so, than treatment with this chemoimmunotherapy.

Treatment Toxicity

The grade 3 or 4 toxicities in patients treated with chemotherapy or chemoimmunotherapy are shown in Table 6. Hematologic suppression was the most common side effect. Twenty-nine percent of patients receiving chemotherapy and 85% of patients receiving chemoimmunotherapy experienced platelet nadirs of less than 100,000/mm^3. Similarly, WBC count nadirs of less than 3,000/mm^3 in these two treatment groups occurred in 20% and 66% of patients, respectively. Mild nausea was a problem for many patients, although it rarely achieved grade 3 toxicity.

The reported side effects of high-dose bolus IL-2 in conjunction with interferon alfa-2b were seen in these patients,[5,6] although these side effects seemed to be transient and resolved within several days after stopping IL-2 and interferon alfa-2b administration. Sixty-five percent of pa-

Table 5. Complete Responses in Patients Receiving Chemotherapy or Chemoimmunotherapy

Patient Age (years) / Sex	Treatment	Date of First Treatment	Site of Tumor	Size of Tumor (cm)	Duration of Response (months)	Current Status as of 4/01/98
55/F	C	1/27/94	Subcutaneous	0.5 × 0.5 1.1 × 1.1 0.9 × 0.9 0.7 × 0.7	38	Alive with disease
37/F	C	3/25/94	Lung Hilum	1.07 × 0.89 5.71 × 3.21	48+	Alive, NED
35/M	C	5/21/94	Lymph node Subcutaneous	4.5 × 3.0 1.75 × 1.25 1.0 × 0.75	46+	Alive, NED
47/F	C	1/15/96	Subcutaneous	1.3 × 1.6 1.8 × 1.7	9	Alive, NED
49/M	CI	2/18/94	Lung (hilum)	2.14 × 2.14	49+	Alive, NED
51/M	CI	3/25/94	Lung Lymph node	1.92 × 1.54 3.46 × 2.31	13	Alive, NED
44/M	CI	3/01/95	Subcutaneous	0.4 × 0.4 0.6 × 0.4	10	Expired with disease

Abbreviations: C, chemotherapy; CI, chemoimmunotherapy; NED, no evidence of disease.

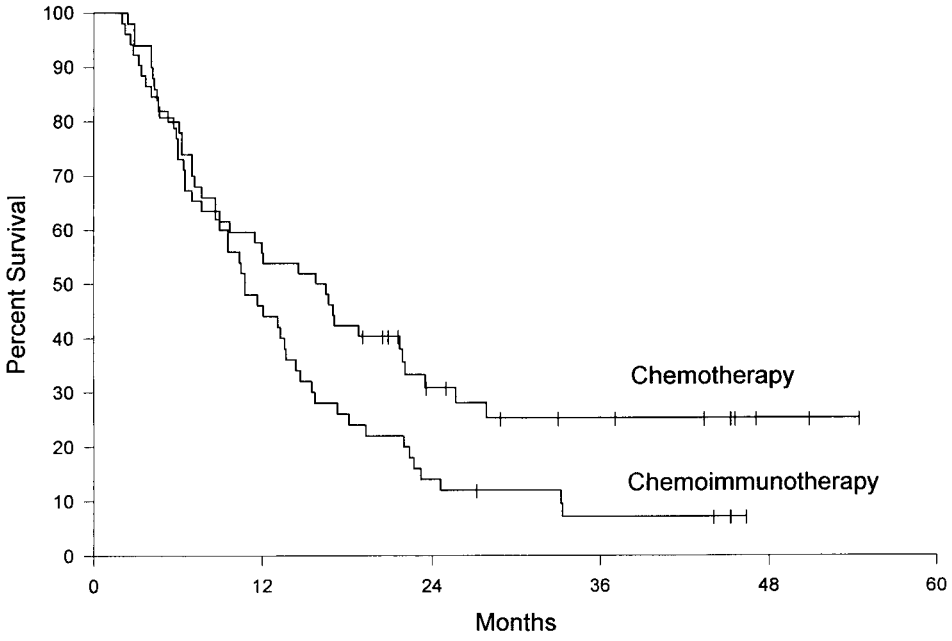

Fig 1. Survival of patients randomized to receive chemotherapy or chemoimmunotherapy (P_2 = .052 favoring chemotherapy).

tients gained more than 5% of their total body weight owing to fluid retention resulting from the capillary permeability leak associated with IL-2 administration. Hepatic and renal dysfunction occurred commonly and were reversible. Hypotension occurred in 23% of patients. There were no treatment-related deaths on the protocol.

DISCUSSION

The median survival of patients with metastatic melanoma in most reported series is between 6 and 12 months.[1,2] In a representative series from a single institution that treated 503 patients with metastatic melanoma over a 13-year period using a variety of single or combination chemotherapeutic regimens, 10 patients (2.0%) achieved a complete response, only three of whom survived more than 5 years; overall, only 10 patients (2.0%) survived more than 5 years.[12] In another representative report of 635 patients who entered onto three sequential Eastern Cooperative Oncology Group studies using single or combination chemotherapies, an 11% incidence of objective responses was seen, and only 10 patients (1.6%) survived beyond 5 years.[13] These characteristic results have led to an intensive search for more effective treatments for patients with metastatic melanoma.

Objective response rates in the range of 10% to 20% have been reported for a large number of single agents, including dacarbazine, the nitrosoureas, vinca alkaloids, cisplatin, dibromodulcitol, and paclitaxel.[1,2] Complete responses are rare, CNS metastases very rarely respond, and there is no convincing evidence that these treatments prolong patient survival. These single-agent studies led to the exploration of a variety of combination chemotherapy regimens, largely stimulated by an early report of 20 patients who received the combination of carmustine (BCNU), dacarbazine, cisplatin, and tamoxifen with a 55% objective response rate.[14] Multiple subsequent studies using this combination or others including agents such as bleomycin and procarbazine reported objective responses in the 30% to 50% range.[1,2] Toxicity in these studies was substantial, however, and hematologic suppression and thromboembolic complications led to a low incidence of treatment-related mortality. In these studies, dacarbazine and cisplatin seemed to be the most active agents, and although BCNU had some activity, it was responsible for significant hematologic suppression. In some studies, tamoxifen was reported to increase objective response rates,[4,9] although, in others, this effect was not seen,[15,16] and it was suspected that tamoxifen played a role in the etiology of thromboembolic complications. In a recent cooperative group study of the treatment of 79 patients with metastatic melanoma using BCNU, dacarbazine, cisplatin, and tamoxifen, an objective response rate of 15% was seen, and this combination was not recommended for the routine treatment of patients with metastatic melanoma.[17] Thus, the question whether combination chemotherapies are superior to the use of single agents remains controversial.

Because of the documented responses of patients with metastatic melanoma to the use of biologic agents such as IL-2 and interferon alfa-2b, enthusiasm has developed recently for the combination of these biologic agents with combination chemotherapy. Several recent reports of these

Table 6. Treatment Toxicity

	Chemotherapy (n = 52, 110 courses)		Chemoimmunotherapy (n = 50, 97 courses)	
	No.	%	No.	%
Grade 3 and 4 side effects				
Chills	2	2	23	24
Pruritus	1	1	9	9
Anaphylaxis	0	0	1	1
Mucositis	0	0	4	4
Nausea	4	4	12	12
Diarrhea	0	0	19	20
Edema	0	0	1	1
Respiratory distress	0	0	2	2
Bronchospasm	0	0	2	2
Pleural effusion	0	0	1	1
Somnolence	0	0	4	4
Coma	0	0	1	1
Orientation	0	0	15	15
Hypotension	0	0	22	23
Angina	0	0	3	3
Arrhythmias	0	0	6	6
Infection	1	1	4	4
Line sepsis	0	0	2	2
Malaise	0	0	39	40
Peak bilirubin (mg/dL)				
0.1-2.0	107	97	61	63
2.1-6.0	3	3	36	37
Oliguria < 80 mL/8 hours	0	0	2	2
Weight gain, % of body weight				
0.0-5.0	102	93	34	35
5.1-10.0	7	6	45	46
10.1-15.0	1	1	12	12
15.1-20.0	0	0	4	4
20.1+	0	0	2	2
Peak creatinine (mg/dL)				
0.1-2.0	104	95	43	44
2.1-6.0	6	5	53	55
6.1-10.0	0	0	1	1
Anemia requiring transfusion, no. of units transfused				
0	103	94	74	76
1-5	7	6	22	23
5-10	0	0	1	1
Platelet nadir (cells/mL)				
0-20,000	1	1	4	4
20,001-60,000	5	5	52	54
60,001-100,000	25	23	26	27
> 100,000	79	72	15	15
WBC nadir (cells/mL)				
301-1,000	0	0	2	2
1,001-3,000	22	20	62	64
3,001-4,000	28	25	26	27
> 4,000	60	55	7	7
Death	0	0	0	0

chemoimmunotherapy regimens have reported objective response rates between 40% and 60%, including complete responses in 10% to 20% of patients.[7-9] However, in a randomized trial comparing the administration of interferon alfa-2b with or without cisplatin, no survival differences were seen.[18] The use of IL-2 and interferon alfa-2b can increase the toxicity of these regimens, and definitive clinical trials demonstrating the superiority of chemoimmunotherapy to chemotherapy alone have not been performed.

Because of the ambiguity surrounding the value of chemoimmunotherapy in the treatment of patients with metastatic melanoma, we designed a prospective randomized trial to compare an aggressive chemoimmunotherapy regimen to chemotherapy alone. The chemotherapy regimen we selected included dacarbazine and cisplatin because of substantial evidence that these are the two most active chemotherapeutic agents for the treatment of patients with melanoma. We did not include BCNU in the treatment regimen because of the low response rates associated with it as a single agent and because of the severe hematologic and immunosuppressive activity due to its use. Tamoxifen was added to the regimen because of the suggestion from several studies that it might increase objective response rates.[4,9] Patients randomized to receive chemoimmunotherapy received IL-2 at high dose (720,000 IU/kg IV every 8 hours) because of our extensive experience demonstrating objective responses, including durable complete responses, with this high-dose regimen.[19] Interferon alfa-2b was administered subcutaneously using a regimen previously reported to be effective when used in combination with chemotherapy. Although many possible chemotherapy and chemoimmunotherapy regimens could have been selected for evaluation, the regimens we selected were aggressive, as evidenced by the toxicities seen, and were designed to take advantage of the best reported responses using each of the two treatment strategies. To reduce bias in this evaluation, all patients were prospectively randomized to one of the two treatments, and all randomized patients are included in this analysis.

The response rate in this series for patients randomized to receive chemotherapy was 27%, compared with 44% in those patients randomized to receive chemoimmunotherapy ($P_2 = .071$). There were four complete responders among patients receiving chemotherapy and three among those receiving chemoimmunotherapy. The more frequent objective responses in chemoimmunotherapy patients were generally of short duration, and 12 of the 23 objective responders receiving this treatment had a response duration of 6 months or less. The tendency toward an increased response rate in patients randomized to receive chemoimmunotherapy did not translate into an increase in overall survival, and there was, in

fact, a trend for a survival advantage in patients receiving chemotherapy alone, compared with those receiving chemoimmunotherapy ($P_2 = .052$). The median survival of patients receiving chemotherapy was 15.8 months, compared with 10.7 months for chemoimmunotherapy patients, and although the median potential follow-up is short (42 months), it is extremely unlikely that any survival advantage will occur in patients randomized to receive chemoimmunotherapy. The short duration of the complete responses in the chemoimmunotherapy group, in fact, suggests that the immunosuppressive properties of the chemotherapy may be inhibiting the durable antitumor effects of IL-2 and interferon alfa-2b. We have recently analyzed a consecutive series of 182 melanoma patients treated with high-dose bolus IL-2 alone by the regimen used in the present combination protocol, and in this study, 27 patients (14.8%) showed objective responses, including 12 patients (6.6%) who had complete responses.[20] Of the 12 complete responders, 10 remained in ongoing complete responses at 59 to 137 months follow-up, and only two patients had recurred at 12 and 16 months, respectively.

It should also be noted that the full six doses of cisplatin were administered in 93% of the treatment courses in patients randomized to receive chemotherapy alone, compared with 75% of the treatment courses in patients receiving chemoimmunotherapy. We have previously reported that the administration of IL-2 and interferon alfa-2b in conjunction with dacarbazine and cisplatin led to the development of hypersensitivity reactions to the chemotherapy agents.[21] These reactions were often manifested by pruritus, erythema, edema, eosinophilia, and hemodynamic instability that limited the administration of cisplatin. The concurrent administration of IL-2 is known to increase sensitivity to other agents, such as radiographic contrast materials.[22] Furthermore, the toxicity resulting from the chemotherapy may have limited the amount of IL-2 that could be administered.

Although there were no treatment-related deaths in the present series, the addition of IL-2 and interferon alfa-2b added substantially to treatment-related toxicity. The major toxicity in the chemotherapy group was hematologic suppression, which was significantly augmented by the addition of immunotherapy. Twenty-nine percent and 85% of patients receiving chemotherapy and chemoimmunotherapy, respectively, had platelet nadirs of less than 100,000/mm^3. Similarly, 20% and 66% of patients receiving chemotherapy or chemoimmunotherapy, respectively, had WBC count nadirs of less than 3,000/mm^3. The transient capillary leak syndrome associated with immunotherapy resulted in a weight gain of greater than 5% in 65% of patients receiving chemoimmunotherapy, compared with a weight gain of greater than 5% in only 7% of patients receiving chemotherapy alone. The toxicities attributable to the addition of immunotherapy were readily reversible, although they did lead to an increase in the duration of patient hospitalization.

Thus, in this prospective randomized trial, we have seen no evidence that the addition of concurrent IL-2 and interferon alfa-2b leads to improvements in the treatment of patients with metastatic melanoma, compared with the combination chemotherapy regimen used alone. These conclusions relate to the specific treatment regimens that we have used and, of course, may not apply to variations of these treatments. It should be emphasized, however, that the doses of dacarbazine, cisplatin, and tamoxifen used in this trial are the same as those used in many trials enthusiastically supporting the use of combination chemotherapy in the treatment of these patients. Similarly, the dose of IL-2 used was the same as that reported to be associated with significant and durable complete responses, and the subcutaneous interferon alfa-2b regimen used is one commonly used in combination with chemotherapy. Because of the increased toxicity seen with the use of immunotherapy in combination with chemotherapy in the treatment of patients with metastatic melanoma, the use of combination chemoimmunotherapy regimens is not recommended unless well-designed prospective randomized trials demonstrate a benefit of this strategy.

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