High-Dose Recombinant Interleukin 2 Therapy for Patients With Metastatic Melanoma: Analysis of 270 Patients Treated Between 1985 and 1993

By Michael B. Atkins, Michael T. Lotze, Janice P. Dutcher, Richard I. Fisher, Geoffrey Weiss, Kim Margolin, Jeff Abrams, Mario Sznol, David Parkinson, Michael Hawkins, Carolyn Paradise, Lori Kunkel, and Steven A. Rosenberg

Purpose: **To determine the short- and long-term efficacy and toxicity of the high-dose intravenous bolus interleukin 2 (IL-2) regimen in patients with metastatic melanoma.**

Patients and Methods: **Two hundred seventy assessable patients were entered onto eight clinical trials conducted between 1985 and 1993. IL-2 (Proleukin [aldesleukin]; Chiron Corp, Emeryville, CA) 600,000 or 720,000 IU/kg was administered by 15-minute intravenous infusion every 8 hours for up to 14 consecutive doses over 5 days as clinically tolerated with maximum support, including pressors. A second identical treatment cycle was scheduled after 6 to 9 days of rest, and courses could be repeated every 6 to 12 weeks in stable or responding patients. Data were analyzed through fall 1996.**

Results: **The overall objective response rate was 16% (95% confidence interval, 12% to 21%); there were 17 complete responses (CRs) (6%) and 26 partial responses (PRs) (10%). Responses occurred with all sites of disease and in patients with large tumor burdens. The median response duration for patients who achieved a CR has not been reached and was 5.9 months for those who achieved a PR. Twelve (28%) of the responding patients, including 10 (59%) of the patients who achieved a CR, remain progression-free. Disease did not progress in any patient responding for more than 30 months. Baseline performance status and whether patients had received prior systemic therapy were the only predictive prognostic factors for response to IL-2 therapy. Toxicities, although severe, generally reversed rapidly after therapy was completed. Six patients (2%) died from adverse events, all related to sepsis.**

Conclusion: **High-dose IL-2 treatment seems to benefit some patients with metastatic melanoma by producing durable CRs or PRs and should be considered for appropriately selected melanoma patients.**

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MELANOMA POSES AN increasingly important health problem. It is estimated that by the end of 1999, the lifetime risk of developing melanoma in the United States will have reached one in 75.[1] Although surgery with or without interferon alfa (IFNα) therapy can be curative in stage I, II, or III disease, a large number of patients will develop distant metastases. Disseminated metastatic disease is associated with a poor prognosis and a mortality rate of more than 95%. In several large series, survival correlated inversely with the number of involved organ sites, visceral involvement, the disease-free interval, and performance status (PS).[2-4] Several treatment options are available to patients with metastatic disease, including single-agent dacarbazine (DTIC) chemotherapy, a variety of combination chemotherapy regimens, and combinations of chemotherapy with tamoxifen or IFNα. DTIC chemotherapy produces responses in approximately 20% of patients, with a median response duration of 4 to 6 months, a 5-year survival rate of 2%, and a median survival time of 6 to 9 months.[5] Although single-institution phase II studies and small phase III trials have shown that combination chemotherapy, or the addition of either tamoxifen or IFNα to DTIC chemotherapy, has potential benefit, no regimen has yet proved superior to DTIC chemotherapy alone.[6-13]

Interleukin 2 (IL-2), a T-cell growth factor, was first identified in 1976,[14] and isolation of the cDNA clone was described in 1983.[15] Subsequently, recombinant IL-2 (rIL-2) was shown to have potent antitumor activity in a number of murine tumor models.[16] Based on animal model data, a high-dose IL-2 regimen was developed in which IL-2 was administered by short intravenous infusion every 8 hours, with or without lymphokine-activated killer cells.[17,18] High-dose bolus IL-2, as a single agent, received United States Food and Drug Administration approval in 1992 after demonstration of durable responses in patients with metastatic renal cell carcinoma.[19] In this report, we describe findings from a recently updated 270-patient database of metastatic melanoma patients treated with the same high-dose IL-2 regimen between 1985 and 1993.

From the Cytokine Working Group and Surgery Branch, National Cancer Institute, Bethesda, MD; Modified Group C Program; and Chiron Corp, Emeryville, CA.

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Address reprint requests to Michael B. Atkins, MD, Division of Hematology and Oncology, Beth Israel Deaconess Medical Center, 330 Brookline Ave, E/KS-158, Boston, MA 02215.

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PATIENTS AND METHODS

Trial Selection

We analyzed all seven National Cancer Institute–sponsored trials and the one Chiron Corp–sponsored trial, all conducted between 1985 and 1993, involving administration of high-dose, single-agent IL-2 (Proleukin [aldesleukin], Chiron recombinant IL-2; Chiron Corp, Emeryville, CA) for the treatment of metastatic melanoma. Data were analyzed through fall 1996 (follow-up, 3 to 11 years). The 270 patients evaluated were entered onto clinical trials conducted at 22 institutions. Participating investigators and study sites are listed in the Appendix. Subgroups of these patients have been described in previous reports.[20-22]

Patient Eligibility

Eligibility criteria varied slightly among studies. In general, eligible patients had to have histologically confirmed, measurable, and clearly progressive metastatic melanoma that was either disseminated or not amenable to local or regional therapy. Patients were required to be 18 years of age and have a good PS (Eastern Cooperative Oncology Group [ECOG], 0 or 1; Karnofsky, 70 to 100) and adequate organ function. Previous chemotherapy, hormonal therapy, radiation therapy, or immunotherapy (including treatment with IFNα, Bacille bilié de Calmette-Guérin, vaccines, and interleukins other than IL-2) was allowed, provided that at least 4 weeks had elapsed since completion of therapy and complete recovery from treatment-related side effects had occurred. Adequate organ function was defined as follows: creatinine concentration $\leq$ 1.5 mg/dL (clearance $>$ 60 mL/min), normal bilirubin concentration, platelet count $\geq$ 100,000/μL, and WBC count 3,500 μL. Patients also had to have adequate pulmonary reserve and be able to receive pressors. The later trials evaluated cardiac and pulmonary parameters more rigorously, using formal pulmonary function testing and cardiac treadmill testing to exclude high-risk patients. All patients were required to give written informed consent.

Patients with a history or symptoms of cardiac disease, antibiotic-requiring systemic infections, coagulation disorders, second malignancies (other than basal cell carcinomas of the skin or stage I carcinoma of the uterine cervix), organ allografts, corticosteroid dependence, infection with the human immunodeficiency virus, hepatitis, or CNS metastases were ineligible in most studies. Patients who were pregnant or nursing were also excluded.

Treatment Plan

IL-2 was administered by 15-minute intravenous infusion every 8 hours for 14 consecutive doses over 5 days, as tolerated. After a 6- to 9-day rest period, an additional 14 doses of IL-2 were scheduled over the next 5 days. Courses of therapy were usually separated by 6- to 12-week intervals. Additional courses of treatment were given to patients who showed evidence of tumor regression or stable disease. A maximum of five treatment courses was permitted.

Dosing

IL-2 doses used were 720,000 IU/kg (44μg/kg; four studies) and 600,000 IU/kg (36μg/kg; three studies). The five patients in the Chiron–sponsored study received 360,000 or 540,000 IU/kg/dose (22 or 33 μg/kg, respectively). Dose modification for toxicity was performed by omitting rather than reducing doses. Doses were generally withheld when the following occurred: hypotension requiring substantial vasopressor support, respiratory distress, cardiac arrhythmias or signs of myocarditis or myocardial ischemia, and neurocortical toxicity manifested as mental confusion or agitation.

Concomitant Medications

Concomitant medications commonly administered included acetaminophen, indomethacin, meperidine, ranitidine, and cimetidine. In addition, hydroxyzine hydrochloride, diphenhydramine, dopamine, phenylephrine hydrochloride, antiemetics, antidiarrheal medications, and sedatives were administered as needed to manage specific side effects. Patients received antibiotics if infection was suspected, and they routinely received diuretics after completion of therapy. Dexamethasone was permitted only for patients with grade 4 life-threatening adverse events unresponsive to other measures.

Adverse-Event Gradations

National Cancer Institute common toxicity criteria were used to grade toxicities. The frequency of on-study deaths and adverse events was determined, and the outcomes of grade 3 and 4 adverse events were analyzed.

Response Criteria and Definitions

All efficacy analyses were performed on an intent-to-treat basis, and all patients who received even a single dose of IL-2 were considered assessable for response. Radiographs of responding patients were centrally reviewed. All bidimensionally measurable lesions were serially evaluated and a total tumor burden was calculated. Criteria to assess complete responses (CRs) and partial responses (PRs) were based on those reported by Oken et al.[23] A CR was defined as the complete disappearance of tumor, including symptoms and laboratory abnormalities associated with tumor, documented on at least two occasions $\geq$ 28 days apart. A PR was defined as a 50% or greater reduction in measurable tumor area (sum of perpendicular diameters of all lesions), with no increase in the size of any lesions, as well as stable symptomatology and laboratory abnormalities, documented on at least two occasions $\geq$ 28 days apart. Response duration was calculated from the initial documentation of best response to the time of progression, the last follow-up evaluation, or death. Survival was calculated from the first dose of IL-2 to the time of death or the last follow-up evaluation. Progression-free survival (PFS) was calculated for responding patients only and was calculated from the first dose of IL-2 to the time of progression, the last documented clinical visit, or death. Response duration and PFS, but not overall survival, were censored at the time that a patient underwent a new intervention (including salvage surgery) for his or her disease. The Kaplan-Meier method[24] was used to analyze these censored time-to-event variables.

Univariate and Multivariate Analyses

Analyses of various demographic and clinical factors were performed in an attempt to determine prognostic factors predictive of response in this population. Potential prognostic factors were evaluated in both univariate and multivariate analyses. Using logistic regression modeling, we calculated odds ratios and 95% confidence intervals (CIs) by the

Table 1. Demographic Summary: All Patients

	No.	%
No. of patients	270	
Age, years		
Median	42	
Range	18-71	
Sex		
Male	174	64
Female	96	36
ECOG PS		
0	191	71
1	74	27
2	5	2
Visceral involvement		
No	84	31
Yes	186	69
Lung	141	52
Liver	77	29
Other	152	56
No. of organ sites		
1	79	29
2	110	41
3	47	17
≥ 4	34	13
Prior therapy for metastatic or unresectable regional disease		
Chemotherapy only	37	14
Immunotherapy only*	51	19
Hormone therapy only	2	1
Combinations of therapies	32	12

*Treatment with IFNα, IFNγ, Bacille bilié de Calmette-Guérin, vaccines, or other interleukins.

profile likelihood method. Factors examined included PS, number of organs involved, visceral involvement, prior systemic therapy, age, sex, and dose-intensity during the first treatment course.

RESULTS

Demographics

The characteristics of the 270 patients as a group are listed in Table 1. Patient characteristics were similar in all eight studies (Table 2). The median patient age was 42 years (range, 18 to 71 years), 174 patients (64%) were men and 96 (36%) were women, and 191 patients (71%) were PS 0, 74 (27%) were PS 1, and five (2%) were PS 2. At least 94% of patients had documented American Joint Committee on Cancer stage IV melanoma, with the remainder having either unspecified-stage disease or stage III disease that was not amenable or resistant to local or regional therapy. The majority of patients (71%) had at least two or more discrete organ sites with metastases at the time of IL-2 treatment, and most patients had multiple lesions within each site. The majority of patients (69%) also had at least one site of visceral disease. The most common site of visceral metastasis was lung (52%). In addition, 29% of patients had liver metastases. Data on prior surgical treatments were recorded for 220 patients, with 96% of these having had prior surgery, including resections of the primary lesions, regional lymph nodes, and/or sites of local or distant re-

Table 2. Demographics for All Patients, by Study

	T84-0524 (84C-220)	T86-0097 (86C-46)	T90-0053 (90C-85)	92C-0094 (92C-94)	T86-0063 (UMCC-8608)	T86-0170 (Cytokine Working Group)	C87-0002 (Modified Group C)	CS-L291-06	Studies Combined	
									No.	%
No. of patients	28	84	32	3	9	64	45	5	270	
Median age, years	44.5	40	39	39	40	45.5	44	38	42	
No. of men	19	53	22	2	4	43	28	3	174	64
No. of women	9	31	10	1	5	21	17	2	96	36
ECOG PS										
0	18	70	24	1	8	36	30	4	191	71
1	9	11	7	2	1	28	15	1	74	27
2	1	3	1	0	0	0	0	0	5	2
Prior therapy										
Radiation	1	10	6	1	2	11	8	0	39	14
Chemotherapy	9	20	8	1	0	15	14	2	69	26
Hormone therapy	0	1	0	0	0	2	3	1	7	3
Immunotherapy	25	24	10	3	1	8	5	4	80	30
Visceral involvement										
No	11	13	10	1	7	20	21	1	84	31
Yes	17	71	22	2	2	44	24	4	186	69
No. of organ sites										
1	8	24	7	0	7	18	15	0	79	29
2	10	32	15	1	2	29	16	5	110	41
3	6	18	4	2	0	11	6	0	47	17
≥ 4	4	10	6	0	0	6	8	0	34	13

NOTE. Values are expressed as median, n, or n (%).

lapse. Thirty-nine (14%) of the 270 patients were reported to have received prior radiation therapy. One-hundred twenty-two (46%) of the patients experienced disease progression during or after systemic therapy, which was generally administered for stage IV disease. Prior systemic treatments included cytotoxic chemotherapy, immunotherapy (other than high-dose IL-2 therapy), combinations of chemotherapy and immunotherapy, and hormonal treatments.

Dosing

One-hundred forty-seven patients received IL-2 720,000 IU/kg every 8 hours (four studies), 118 patients received 600,000 IU/kg every 8 hours (three studies), and five patients received either 360,000 or 540,000 IU/kg. Patients treated with the higher doses of IL-2 received fewer doses; consequently, the median cumulative amount of IL-2 for the first course of therapy was similar for each dose level (Table 3). Clinical factors such as PS did not influence the amount of IL-2 delivered. Patients received up to five courses of therapy (mean, 1.4 courses; median, one course), with 81 patients receiving more than one treatment course. Information on the number of patients treated and the amount of IL-2 administered per treatment course is listed in Table 4.

Efficacy

The overall response rate was 16% (95% CI, 12% to 21%). There were 17 CRs (6%) and 26 PRs (10%) (Table 5). Responses were noted in the lung, liver, lymph nodes, spleen, and adrenal, in soft tissue and bone, and in cutaneous and subcutaneous sites. Characteristics of the 43 responding patients are listed in Tables 6 and 7.

The median duration of response for all responders was 8.9 months. Response duration curves according to response classification are displayed in Fig 1. The median response duration for patients who achieved a CR has not been reached, with 10 of the 17 CRs ongoing at 24 to 106 months. The median duration of PRs was 5.9 months. Two patients who achieved a PR had ongoing responses of 55 and 92 months' duration. Although these patients were classified as achieving a PR and had persistent scan abnormalities at follow-up evaluations, they remained progression-free without further treatment. The median PFS time for all responding patients was 13.1 months. The median PFS time for patients who achieved a CR has not yet been observed but is at least 54 months. Fifty-eight percent of the responders remained progression-free at 12 months. The median PFS time for the patients who achieved a PR was 8.3 months. In 37% of the PR, the PFS time exceeded 12 months. There were no relapses in responding patients after 30 months.

Two of the seven patients who achieved a CR and who relapsed maintained complete remission in visceral organ sites (lung, liver, adrenal) while relapsing in lymph node and soft tissue, respectively. Their PFS times were 6.6 and 14.9 months, respectively. Disease at these sites of relapse was treated with local therapy, which rendered these patients again disease-free. These two patients were alive and disease-free 53.7 and 64.1 months after therapy, respectively. In addition, in four of the patients who achieved a PR and had disease subsequently progress at a single site, surgical resection (three patients) or radiation therapy (one patient) was successful. These patients were alive 66.0, 87.2, and 103.6 months (surgical resection) and 60.1 months (radiation) after treatment. Overall, 15 responding patients had surgery or radiation therapy after IL-2 treatment, and five of these patients are currently disease-free. Information on these patients is listed in Table 8.

Responses were seen in several patients who had received prior systemic therapy. Seven responding patients had received prior chemotherapy. Two of these seven patients

Table 4. Dosing by Course Number

Course No.	No. of Patients	Median Total No. of Doses	Median Cumulative IL-2 Dose (MIU/kg)
1	270	18.0	12.2
2	81	15.0	10.8
3	25	14.0	10.1
4	7	14.0	8.6
5	3	10.0	7.2

Table 3. Treatment Administered

IL-2 Dosage (IU/kg)*	No. of Patients	Median No. of Doses in Course 1	Median Cumulative IL-2 in Course 1 (MIU/kg)
720,000	147	16	11.5
600,000	118	22	13.2
360,000 or 540,000	5	26	9.8
All patients	270	18	12.2

*Every 8 hours for 14 doses, days 1 through 5 and 15 through 19.

Table 5. Summary of Efficacy

Response	No.	%	Response Duration (months) Median	Range
CR	17	6	*	2.5-106.2†
PR	26	10	5.9	1.5-91.5†
PR and CR	43	16	8.9	1.5-106.2†

*Not yet reached; more than 40 months in fall 1996.

†Ongoing response.

Table 6. Characteristics of Patients Who Achieved a Complete Response

Patient No.	AJCC Stage	ECOG PS	Baseline Tumor Burden (cm^2)	Response Duration (months)	Site(s) of Tumor Regression
014KC	4	1	15.0	2.5	Subcutaneous sites, lymph node, lung, liver
E495	4	0	Assessable*	6.2	Lung
IL657	4	0	6.6	6.4	Lung
N1339382	4	1	127.4	8.3	Subcutaneous sites, lung, liver
N1335454	4	0	23.7	8.9	Lymph node
IL499	4	0	25.0	12.9	Subcutaneous sites, lung, adrenal
E180206483	4	0	61.8	18.2	Subcutaneous sites, lymph node, kidney, perihepatic, perirenal
IL610	4	0	15.2	24.1†	Subcutaneous sites
IL595	4	0	34.8	40.5†	Subcutaneous sites, lung
IL592	4	0	7.3	41.2†	Subcutaneous sites, lymph node, lung
IL451	4	0	14.0	59.1†	Lymph node, lung
IL392	4	0	16.9	61.9†	Lymph node
IL321	4	0	63.9	65.3†	Subcutaneous sites, lymph node
IL277	3	0	Assessable*	72.3†	Cutaneous
H9	4	0	3.1	86.3†	Subcutaneous sites, lymph node, lung
C016	4	0	6.5	106.2†	Cutaneous sites, lymph node, lung
IL006	4	1	63.5	102.7†	Subcutaneous sites, lymph node, lung

Abbreviation: AJCC, American Joint Committee on Cancer.

*Assessable: multiple small lesions too numerous to count.

†Ongoing response.

Table 7. Characteristics of Patients Who Achieved a Partial Response

Patient No.	AJCC Stage	ECOG PS	Baseline Tumor Burden (cm^2)	Response Duration (months)	Site(s) of Tumor Regression
E439	4	0	19.2	1.5	Subcutaneous sites, lymph node
IL317	4	2	230.3	2.1	Subcutaneous sites, lymph node, kidney
E483	4	0	69.5	2.1	Subcutaneous sites, lymph node
N1375055	4	0	32.4	2.1	Subcutaneous sites, lymph node, lung
IL340	4	0	3.8	2.1	Subcutaneous sites
E132169056	4	0	39.8	3.2	Lymph node, lung, liver
908473	4	0	5.0	3.3	Lymph node
CO40	4	0	76.3	3.4	Subcutaneous sites, lymph node, adrenal
IL066	4	0	20.1	3.5	Subcutaneous sites, lung
IL526	4	0	5.6	3.8	Lymph node, liver
IL470	4	0	94.6	3.9	Lymph node, lung, adrenal
IL190	4	0	10.0	4.2	Subcutaneous sites, lymph node
E470	4		4.4	5.7	Lymph node
E499	4	0	98.8	6.0	Subcutaneous sites, lymph node, soft tissue, lung
IL255	3	0	Assessable*	6.6	Cutaneous sites, subcutaneous sites
IL027	3	1	20.5	7.4	Cutaneous sites
IL290	4	1	81.6	8.2	Lymph node
IL045	4	0	36.8	9.5	Lung, liver
CO82	4	0	25.9	12.5	Subcutaneous sites, lymph node, soft tissue, lung, bone
E431	4	1	100.0	14.0	Adrenal
IL418	4	0	7.3	16.8	Lung, liver
IL316	3	0	0.7	18.4	Cutaneous sites
IL413	4	0	25.3	29.5	Subcutaneous sites, lymph node, lung
E131307472	4	0	37.7	6.4†	Subcutaneous sites, liver
009KB	4	0	50.7	54.9†	Lymph node, lung, liver
CO76	4	0	29.4	91.5†	Lymph node, lung, liver, spleen

*Assessable: multiple small lesions too numerous to count.

†Ongoing response.

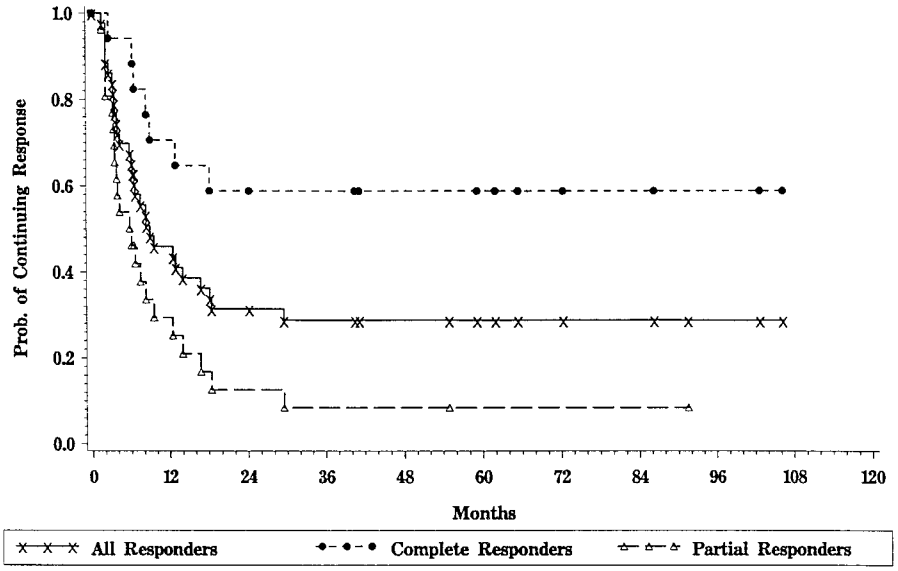

Fig 1. Kaplan-Meier plots of response durations for patients who achieved a CR, a PR, or any response.

and one other responding patient had received prior IFN therapy (two IFNα therapy, one IFNγ therapy). Seven additional responding patients had previously received another type of immunotherapy.

The median survival duration (Kaplan-Meier) for all 270 patients was 11.4 months (Fig 2). With a median follow-up of 62 months, 20 (47%) of the responding patients were still alive, 15 having survived more than 5 years.

Assessment of Risk Factors

Of the multiple prognostic factors analyzed, only two, ECOG PS and prior systemic therapy, were associated with response (Table 9). Baseline ECOG PS was predictive of response, with the rate of objective responses among patients with a PS of 0 being twice that among patients with a PS of 1 (19% *v* 9%). The unadjusted odds ratio for response was 0.42 (95% CI, 0.16 to 0.93). In addition, the PS

Table 8. Salvage Surgery or Limited-Site Radiation Therapy in Responding Patients

Patient No.	Response	Response Duration (months)	Initial Disease Site(s)	Site(s) of Progression	Status in 1996	Local Therapy	Overall Survival Time (months)
N1335454	CR	8.9	Lymph node	Subcutaneous, gastrointestinal	Dead	Surgery	16.8
N1339382	CR	8.3	Subcutaneous sites, liver, lung	Soft tissue, CNS	Dead	Surgery	36.8
IL657	CR	6.4	Lung	CNS	Dead	Surgery	20.7
IL499	CR	12.9	Subcutaneous sites, lung, adrenal	Soft tissue	Alive	Surgery	64.1*
014KC	CR	2.5	Subcutaneous sites, lymph node, lung, liver	Portacaval, nasal	Alive	Surgery	53.7*
C082	PR	12.5	Subcutaneous sites, lymph node, soft tissue, lung, bone	Subcutaneous	Alive	Surgery	87.2*
908473	PR	3.3	Lymph node	Lymph node	Alive	Surgery	103.6*
E431	PR	14.0	Adrenal	Adrenal, liver, lung	Dead	Surgery	24.9
E132169056	PR	3.2	Lymph node, lung, liver	CNS, bone	Dead	Surgery	23.2
N1375055	PR	2.1	Subcutaneous sites, lymph node, lung	Lung, CNS	Dead	Surgery	12.4
IL066	PR	3.5	Subcutaneous sites, lung	Lymph node	Dead	Surgery	14.2
IL413	PR	29.5	Subcutaneous sites, lymph node, lung	Lung	Dead	Surgery	47.4
IL340	PR	2.1	Subcutaneous sites	Subcutaneous	Dead	Surgery	61.7
IL470	PR	3.9	Lymph node, lung, adrenal	Subcutaneous	Alive	Surgery	66*
IL418	PR	16.8	Lung, liver	CNS	Alive	Brain radiation therapy	60.1*

*Ongoing response.

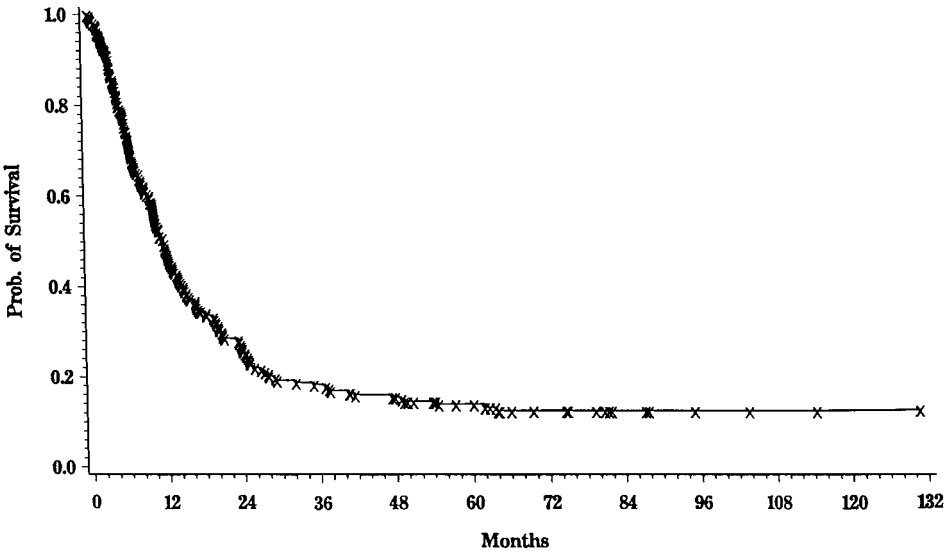

Fig 2. Kaplan-Meier plot of survival for the whole study population (270 patients).

0 group had 14 of the 17 CRs. Although patients with a PS of 1 or 2 were less likely to respond, the duration of response was not different from that among patients with a PS of 0. The objective response rate among patients who had not received prior systemic therapy was twice that among patients who had received prior systemic therapy (21% *v* 10%). Fifteen of the 17 patients who achieved a CR had not received prior systemic treatment. The pattern of metastatic involvement was not associated with response. Patients had responses in virtually all organ sites, including lung, liver, adrenal, kidney, spleen, and bone, although only two patients with ongoing responses, both PRs, had hepatic metastases.

Toxicity

Toxicities among the 270 patients are listed by organ system in Table 10. The events reported are similar to those previously reported in the metastatic renal cell patients who received the same regimen.[19] Most of the severe toxicities resembled the clinical manifestations of septic shock. Hypotension was the most common toxicity and occurred in 64% of patients, with grade 4 hypotension reported in 1%. Supraventricular tachycardia was reported in 17% of patients, but life-threatening ventricular tachycardias occurred in less than 1% of patients. Grade 4 respiratory events, including adult respiratory distress syndrome and respiratory failure, occurred in 4%. Nausea, vomiting, and diarrhea were common, but life-threatening gastrointestinal side effects were rare. Mental status changes were also common and could be severe; 2 patients (1%) experienced grade 4 coma. Elevations of creatinine levels were common, but all patients recovered renal function after completion of therapy. Grade 4 increases in bilirubin levels were observed in 2% of patients, but these abnormalities were not considered dose limiting and did not lead to chronic liver dysfunction. Infections were reported in 15% of patients, with life-threatening infections or sepsis occurring in 3%.

Table 9. Subset Analysis: Response

Prognostic Factor	Unadjusted Odds Ratio	95% CI
ECOG PS	0.42	0.16-0.93
Prior systemic therapy	0.41	0.19-0.81
Visceral involvement	0.64	0.33-1.28
No. of organ sites	1.44	0.69-3.23
Dose intensity of course 1	1.36	0.71-2.69
Sex	0.82	0.42-1.62
Age	0.86	0.44-1.65

Six (2.2%) of 270 patients died from treatment-related toxicity. Five of the six patients were entered onto the study with a PS of 1 and one was entered with a PS of 0. Most deaths were the result of multiple medical complications; however, bacterial sepsis was the principal cause of death in all. Gram-positive organisms were identified in five of the six patients, including *Staphylococcus aureus* in three patients. None of these patients received prophylactic antibiotic therapy during IL-2 treatment. No treatment-related deaths occurred in the 88 patients treated after 1990, when antibiotic prophylaxis became routine for patients receiving high-dose IL-2 therapy.

DISCUSSION

Clinical and laboratory observations have suggested that host immunologic mechanisms can influence the course of melanoma and have stimulated interest in the use of biologic

Table 10. Incidence of Most Common and Most Severe Adverse Events

Event	Incidence (%)		
	Grade 3	Grade 4	All Grades
Cardiovascular			
Hypotension	44	1	64
Tachycardia			
Supraventricular	1	0	17
Ventricular	1	1	1
Myocardial infarction	0	1	1
Myocardial ischemia	2	< 1	4
Gastrointestinal			
Nausea	6	0	24
Vomiting	34	3	55
Diarrhea	29	3	54
Stomatitis	1	< 1	14
Neurologic			
Confusion	13	0	30
Somnolence	3	0	17
Coma	0	1	1
Pulmonary			
Dyspnea	9	1	31
Adult respiratory distress syndrome, pulmonary edema	5	4	16
Hepatic			
Elevated bilirubin levels	7	2	51
Elevated transaminase levels	6	1	39
Elevated alkaline phosphatase levels	1	< 1	13
Renal			
Oliguria	30	9	49
Increased creatinine levels	1	0	35
Anuria	0	8	8
Hematologic			
Thrombocytopenia	16	1	43
Anemia	1	< 1	29
Leukopenia	1	< 1	21
Skin			
Rash	2	0	27
Exfoliative dermatitis	0	0	15
General			
Fever and/or chills	18	1	47
Malaise	14	0	34
Infection	9	2	15
Sepsis	1	1	2

response modifiers to treat this disease. IFNα therapy has produced response rates in the 15% to 20% range.[25] The majority of responses to IFNα therapy have occurred in patients with subcutaneous and small-volume disease, presaging its eventual role in the high-risk adjuvant setting.[26] High-dose IL-2 therapy has also been reported to produce responses in up to 20% of patients with metastatic melanoma treated in various phase II trials.[20,21,27] Although major tumor regressions and durable responses have been reported with a variety of treatment schedules, a composite, multi-institutional, long-term follow-up analysis of patients treated with a single IL-2 regimen has not been previously presented.

In this analysis of data from 270 patients with metastatic melanoma pooled from eight protocols carried out at 22 institutions, high-dose IL-2 therapy produced a modest response rate. Unlike the responses to other agents or regimens used in the treatment of metastatic melanoma,[28,29] many of the responses to this high-dose IL-2 regimen were durable. The median duration for CRs in this series of patients has not been reached but is more than 40 months, and the median PFS time for the entire group of responding patients is more than 1 year. Furthermore, there were no relapses in responding patients after 30 months, suggesting that in many of these patients, disease may never recur. The clinical responses in this report were also remarkable because they were not limited to patients with only good-risk features. In the logistic regression analysis for response, there was no association between response and visceral involvement or the number of organ sites with metastatic disease. Although most of the durable responses occurred in patients with lymph node, lung, or skin involvement and ECOG PS of 0, there were a few long-term responders with visceral disease, such as disease involving liver or kidney, and/or ECOG PS of ≥ 1.

Responses were less frequent in patients who had received prior systemic therapy. The fact that in a large proportion of these patients, prior therapy included immunotherapy, which conceivably could have been cross-resistant, may partially explain this finding. Because very few patients had previously received IFNα therapy, it is unclear how the clinical activity of high-dose IL-2 therapy would be influenced by the current extensive use of IFNα treatment in the adjuvant setting. Finally, no statement can be made on various biologic or clinical factors that might correlate with response, because these factors were not routinely measured in all trials.

Five responding patients who developed isolated relapses or sites of progression were rendered disease-free with resection of these residual lesions and remained alive and disease-free for up to 8.5 years after surgery. Thus, it seems that second-line surgery might be beneficial in selected patients whose disease has progressed in sites where surgical resection is possible.

The results with this high-dose IL-2 regimen in patients with metastatic melanoma were remarkably similar to the results seen in patients with metastatic renal cell carcinoma with respect to response rate, durability of responses, and the role of salvage surgery.[19] In addition, the toxicity profile was very similar in the patient groups. Melanoma patients treated

with this regimen experienced significant morbidity; however, nearly all toxicities were rapidly reversible, and long-term sequelae from this treatment were extremely rare.

Over the 8 years encompassed in this series, much has been learned about appropriate patient selection for high-dose IL-2 therapy and toxicity management that has enhanced the safety of this treatment.[30,31] For example, routine screening with exercise or thallium stress tests and pulmonary function tests has led to the exclusion of higher-risk patients with pre-existing cardiopulmonary disease. In addition, a better understanding of the durability of tumor responses has encouraged the limiting of therapy to two or three courses for patients exhibiting major responses. The importance of selecting patients with a good PS has also become apparent, because PS is predictive of response and may predict for risk of severe toxicity. Five of the six treatment-related deaths in our series occurred in patients who began treatment with a PS of 1. Mortality in this series was also closely tied to the occurrence of bacterial sepsis. With the identification of the IL-2– associated neutrophil chemotactic defect[32] and the consequent routine use of antibiotic prophylaxis, serious infectious complications have become infrequent.[33] Nonetheless, high-dose IL-2 treatment remains a difficult treatment regimen and should be restricted to appropriately selected patients treated by experienced clinicians at established treatment centers.

In the 13 years that IL-2 therapy has been studied in patients with metastatic melanoma, a great deal has been learned about the mechanisms of efficacy and toxicity associated with high-dose IL-2 therapy, which might lead to more active and/or tolerable treatment regimens. IL-2 has been investigated in combination with a variety of other drugs aimed at dissociating the toxic effects of therapy from the antitumor effect.[34-38] Although results in these studies have been disappointing to date, investigations continue with more promising toxicity-reducing agents.[39] Although lower-dose, less toxic IL-2 regimens have shown some activity in renal cell carcinoma,[40-43] similar results have not been noted in metastatic melanoma.[27] However, results have been encouraging in studies in which cisplatin-based chemotherapy was combined with either high-dose IL-2 therapy alone or lower doses of IL-2 combined with IFNα therapy.[13,44] Some of these regimens may be safe enough to use in community hospital[45-47] or even outpatient settings.[48] Although response rates with these biochemotherapy combinations have been impressive, proof of their superiority to either IL-2 therapy alone or chemotherapy alone awaits the completion of ongoing randomized phase III trials.[49] Phase I/II studies with vaccines using peptide antigens recognized by T lymphocytes are also now under way. Some of these vaccines have produced encouraging results when combined with high-dose IL-2 therapy,[50] an effect that also awaits confirmation in studies involving larger numbers of patients. Although the optimal treatment regimen for metastatic melanoma has yet to be defined, the durable responses observed with IL-2–based therapy make it likely that this agent will continue to play a pivotal role in the treatment of this disease.

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APPENDIX

List of Investigators

Name	Center	Study No.
Abrams, J.	University of Maryland Cancer Center, University of Maryland Hospital, Baltimore, MD	T86-0063 (UMCC-8608)
Atkins, M.	New England Medical Center, Boston, MA	T86-0170
Bast, R.	Duke University Medical Center, Durham, NC	C87-0002
Cassidy, J.	National Institutes of Health, Surgery Branch, National Cancer Institute, Bethesda, MD	92C-0094 (92C-94)
Crum, E.	Case Western Reserve University, University Hospital of Cleveland, Cleveland, OH	C87-0002
Doroshow, J.	City of Hope Medical Center, Duarte, CA	T86-0170, C87-0002
Dutcher, J.	Albert Einstein School of Medicine, Montefiore Medical Center, Bronx, NY	C87-0002
Ettinger, D.	Johns Hopkins University, Baltimore, MD	C87-0002
Fefer, A.	Fred Hutchinson Cancer Research Center, Seattle, WA	C87-0002
Fisher, R.	Loyola University, Maywood, IL	T86-0170
Fleischman, J.	Cleveland Metroplitan General Hospital, Cleveland, OH	C87-0002

APPENDIX
List of Investigators (Cont'd)

Name	Center	Study No.
Fox, K.	University of Pennsylvania Hospital, Philadelphia, PA	C87-0002
Glick, J.	University of Pennsylvania Hospital, Philadelphia, PA	C87-0002
Hawkins, M.	Investigational Drug Branch, Cancer Therapy Evaluation, Modified Group C Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD	C87-0002
Krakoff, I.	M.D. Anderson Cancer Center, Texas Medical Center, Houston, TX	C87-0002
Kim, B.	Case Western Reserve University, University Hospital of Cleveland, Cleveland, OH	C87-0002
Lotze, M.	National Institutes of Health, Surgery Branch, National Cancer Institute, Bethesda, MD	T84-0524, (84C-220)
Lotze, M.	University of Pittsburgh Medical Center, Pittsburgh, PA	CS-L291-06
Margolin, K.	City of Hope Medical Center, Duarte, CA	T86-0170, C87-0002
Marshall, E.	Albert B. Chandler Medical Center, University of Kentucky, Lexington, KY	C87-0002
Parkinson, D.	Tufts, New England Medical Center Hospital, Boston, MA	T86-0170
Prasthofer, E.	University of Alabama at Birmingham, L.B.W. Tumor Institute, Birmingham, AL	C87-0002
Rayner, A.	University of California San Francisco Medical Center, San Francisco, CA	T86-0170
Redman, B.	Wayne State University, Harper-Grace Hospitals, Detroit, MI	C87-0002
Rosenberg, S.	National Institutes of Health, Surgery Branch, National Cancer Institute, Bethesda, MD	T84-0524 (84C-220), T86-0097 (86C-46), T90-0053 (90C-85)
Samlowski, W.	University of Utah Medical Center, Salt Lake City, UT	C87-0002
Stewart, J.	University of Vermont, Burlington, VT	C87-0002
Sznol, M.	National Institutes of Health, Surgery Branch, National Cancer Institute, Bethesda, MD	T86-0170
Todd, M.	Yale Comprehensive Cancer Center, Yale University School of Medicine, New Haven, CT	C87-0002
Vogelzang, N.	University of Chicago, Chicago, IL	C87-0002
Weiss, G.	University of Texas, San Antonio, San Antonio, TX	T86-0170
Wiernik, P.	Albert Einstein School of Medicine, Montefiore Medical Center, Bronx, NY	T86-0170, C87-0002
Yang, J.	National Institutes of Health, Surgery Branch, National Cancer Institute, Bethesda, MD	T90-0053, (90C-85)

NOTE. Curriculum vitae of these investigators are available upon request.

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