Impact of the Number of Treatment Courses on the Clinical Response of Patients Who Receive High-Dose Bolus Interleukin-2

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Purpose: **To determine the impact of treatment with successive courses of high-dose bolus interleukin-2 (IL-2) on the incidence of clinical responses in patients with metastatic melanoma or renal cell cancer.**

Patients and Methods: **A consecutive series of 350 patients with either metastatic melanoma or renal cell cancer who were treated with high-dose bolus IL-2 in the Surgery Branch, National Cancer Institute, between September 1985 and November 1996 was analyzed, with a median potential follow-up of 7.1 years. All patients were treated with 720,000 IU/kg of IL-2 administered by a 15-minute intravenous infusion every 8 hours for up to 5 days, as clinically tolerated per cycle. Patients were retreated according to clinical response and tolerance to the IL-2 therapy.**

Results: **Of the 149 patients with melanoma, 10 achieved complete responses (CRs) and 13 partial responses (PRs), for an overall response rate of 15.4%. Of the 201 patients with renal cell cancer, 18 achieved CRs and 20 PRs, for an overall response rate of 19.0%. Among responding patients, 21 of 23 with melanoma and 34 of 38 with renal cell cancer developed at least PRs after the first course of IL-2.**

Conclusion: **Most patients with metastatic melanoma and renal cell cancer who achieved PRs or CRs to intravenous high-dose bolus IL-2 were identified after the first course of therapy. Those who demonstrated no response after two treatment courses failed to respond to additional IL-2 therapy. Based on this retrospective analysis, we recommend that patients who exhibit objective responses to treatment with high-dose bolus IL-2 receive additional treatment courses until either CR or IL-2 intolerance develops. Patients who do not achieve objective responses after two courses of IL-2 should receive no further treatment with this regimen.**

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PATIENTS WITH metastatic melanoma or renal cell cancer have a median survival of less than 1 year, and in the absence of effective treatment, almost all eventually succumb to their disease. The administration of interleukin-2 (IL-2) causes complete responses (CRs) or partial responses (PRs) in approximately 15% of patients with metastatic melanoma and in 19% of patients with renal cell cancer.[1] Approximately one half of these represent durable CRs. In May 1992, IL-2 was licensed by the Food and Drug Administration for use in the treatment of patients with metastatic renal cell cancer. IL-2 was approved for treating patients with metastatic melanoma in February 1998.

At the National Cancer Institute, Surgery Branch, we began to treat patients with high-dose bolus recombinant IL-2 alone in September 1985.[2-4] Since that time, 350 consecutive patients have been treated with this regimen. These patients were observed for a median of 7.1 years as of March 1998. The longest CR, which was ongoing at the time of this writing, was 12.4 years.[1] This unique population was analyzed to determine the tempo of the clinical responses in patients treated with high-dose bolus IL-2 alone to identify the antitumor effects of successive courses of immunotherapy. In addition, because IL-2 can be associated with significant toxicity, we hoped to elucidate a reasonable strategy for patient treatment in this clinical setting.

PATIENTS AND METHODS

Patients

The study population consisted of a consecutive series of 350 patients treated at the Surgery Branch, National Cancer Institute between September 1985 and November 1996. All patients had clinically progressive metastatic renal cancer or melanoma and had received no other therapy for at least 30 days before entering onto the treatment protocol. The protocols were approved by the Institutional Review Board of the National Cancer Institute, and all patients provided informed consent. Response to treatment and survival were continuing to be assessed in all patients as of March 1998, with a median potential follow-up of 7.1 years.

Patients who had received prior IL-2 or who had evidence of concomitant severe respiratory, cardiovascular, or renal disease were not accepted into these trials. Before entry onto the protocol, all patients were evaluated with computed tomographic (CT) or magnetic resonance imaging scans of the brain, CT scans or full-lung tomograms of the lungs, abdominal CT scans, and radionuclide bone scans. Patients were not eligible if they had CNS metastases. All participants

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Table 1. Patient Characteristics

	Melanoma		Renal Cell		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Total patients	149	100	201	100	350	100
Sex						
Male	99	66	138	69	237	68
Female	50	34	63	31	113	32
Age group						
11-20 years	3	2	1	0	4	1
21-30 years	21	14	10	5	31	9
31-40 years	52	35	27	13	79	23
41-50 years	37	25	69	34	106	30
51-60 years	25	17	71	35	96	27
61-70 years	11	7	23	11	34	10
Race						
Asian	0	0	1	0	1	0
Black	1	1	8	4	9	3
Hispanic	0	0	2	1	2	1
Other	4	3	8	4	12	3
White	144	97	182	91	326	93
Performance status						
0	117	79	146	73	263	75
1	26	17	44	22	70	20
2	6	4	10	5	16	5
3	0	0	1	0	1	0
Prior therapy						
None	2	1	7	3	9	3
Surgery	144	97	192	96	336	96
Chemotherapy	39	26	13	6	52	15
Radiotherapy	20	13	18	9	38	11
Hormonal	1	1	7	3	8	2
Immunotherapy	60	40	32	16	92	26
Any two or more	79	53	54	27	133	38
Any three or more	31	21	14	7	45	13

in the trial underwent stress ECG or stress radionuclide ejection or thallium scans, except for a few patients who were entered early onto the protocol. Patients with evidence of ischemic heart disease or significant arrhythmias were not eligible.

Treatment

Recombinant IL-2 (supplied by Cetus Oncology Division, Chiron Corporation, Emeryville, CA) was administered intravenously over 15 minutes at a dose of 720,000 IU/kg. IL-2 was reconstituted from a lyophilized powder with 1.2 mL of sterile water per vial. Vials also contained 5% mannitol and approximately 130 mg of sodium dodecyl sulfate per milligram of IL-2. A dilution of IL-2 in 50 mL of normal saline containing 5% human serum albumin was used for infusion. Patients received IL-2 every 8 hours. Patients with evidence of stable or responding disease were eligible to receive a second course of treatment. IL-2 was routinely administered in a general surgery ward, although some patients required transfer to the intensive care unit for monitoring or administration of vasopressors. All patients received medications such as acetaminophen and indomethacin to prevent the side effects associated with IL-2 administration.[4,5]

Evaluation of Response

Metastatic tumor deposits were measured with either radiologic studies or physical examination, and the product of maximal perpendicular tumor diameters was calculated. Measurements were taken before treatment, 2 months after treatment, and at regular intervals thereafter. A PR was defined as a 50% or greater reduction in the sum of products of the perpendicular diameters of all lesions that lasted at least 1 month with no new or growing lesions. A CR was defined as the complete disappearance of all disease without the appearance of any new disease for at least 1 month. A minor response (MR) was defined as having a 25% to 49% reduction in tumor burden. Anyone who did not achieve at least a 25% reduction in disease was considered to have no response to treatment. Response and survival durations were calculated from the time of the first dose of IL-2.

RESULTS

Patient Characteristics

Between September 1985 and November 1996, 350 patients (149 with metastatic melanoma and 201 with metastatic renal cell cancer) received therapy with high-dose bolus IL-2 in the Surgery Branch, National Cancer Institute (Table 1). Most patients ranged between the ages of 21 and 60 years. The male-to-female ratio was approximately 2:1. The study population was heavily pretreated.

Table 2. Response of Patients Treated with High-Dose Bolus IL-2

Diagnosis	Total No. of Patients	CR		PR		Total Responses	
		No. of Patients	%	No. of Patients	%	No. of Patients	%
Melanoma	149	10	6.7	13	8.7	23	15.4
Renal cancer	201	18	9.0	20	10.0	38	19.0
Total	350	28		33		61	17.4

Thirty-eight percent of the patients had received two or more treatments each for their cancer, and 13% had received three or more different treatments each.

Response to Therapy

The response rates to high-dose IL-2 in the study population are presented in Table 2. Of the 149 melanoma patients, 10 achieved CRs and 13 PRs, for an overall response rate of 15.4%. Of the 201 patients with renal cell cancer, 18 experienced CRs and 20 PRs, for an overall response rate of 19.0%. Thus, of the 350 patients, 28 achieved CRs and 33 PRs, for an overall response rate of 17.4%.

Tempo of Response

Patient responses after the administration of each course of IL-2 for patients with melanoma or renal cell cancer are presented in Tables 3 and 4. For courses 2 through 4, patients are listed according to their clinical response to prior courses of therapy. In the melanoma cohort (Table 3), 21 of 149 patients developed clinical responses (18 PRs and 3 CRs) to the first course of therapy. Seventeen patients who achieved PRs to course 1 went on to receive a second course of therapy. Among these, one patient developed a CR. Forty-three patients who showed no response to course 1 of IL-2 received a second course of therapy, and two of these developed PRs. Eight patients who showed no response to courses 1 and 2 of IL-2 received a third course of therapy, and none of these patients responded. Eleven patients who achieved PRs after two courses of IL-2 received a third course of therapy, and one of these patients developed a CR. All 23 patients who sustained objective responses to high-dose IL-2 developed at least PRs after two courses of therapy.

In the renal cell cancer cohort (Table 4), 34 of 201 patients achieved objective responses (30 PRs and 4 CRs) and one developed an MR to the first course of therapy. Twenty-eight patients who achieved PRs to course 1 received a second course of therapy, with three of these developing CRs. The patient who sustained an MR achieved a PR after course 2 of high-dose IL-2. Sixty-three patients who showed no response to course 1 received a second course of therapy, and two of these developed PRs and one an MR. Nine patients who had not responded to two courses received a third course, and none developed an objective response. The one patient with an MR after two courses was retreated and achieved a CR. Twenty-one patients who had PRs after two courses of IL-2 received a third course of therapy, and eight of these developed CRs. Seven patients with PRs after three courses of therapy received a fourth course of treatment, and two of these achieved CRs. All but one of the 38 patients with renal cell cancer who sustained objective responses to high-dose IL-2 had developed at least PRs after two courses of therapy.

The duration of CR was analyzed in both melanoma and renal cell cancer. The duration of CR was not related to whether a CR was attained after the first course of IL-2 or

Table 3. Response to Successive Courses of High-Dose IL-2 in Patients With Metastatic Melanoma

	Response to Course 1			
No. of patients treated with course 1 (n = 149)	NR 128	MR 0	PR 18	CR 3
	Response to Course 1			
No. of patients treated with second course (n = 63)	NR 43		PR 17	CR 3
Response to courses 1 and 2				
NR	41		—	—
MR	—		—	—
PR	2		16	—
CR	—		1	3
	Response to Courses 1 and 2			
No. of patients treated with third course (n = 20)	NR 8		PR 11	CR 1
Response to courses 1-3				
NR	8		—	—
MR	—		—	—
PR	—		10	—
CR	—		1	1
	Response to Courses 1-3			
No. of patients treated with fourth course (n = 4)	NR 1			PR 3
Response to courses 1-4				
NR		1		—
PR		—		3
CR		—		—

Abbreviation: NR, no response.

Table 4. Response to Successive Courses of High-Dose IL-2 in Patients With Metastatic Renal Cell Cancer

	Response to Course 1			
No. of patients treated with course 1 (n = 201)	NR 166	MR 1	PR 30	CR 4
	Response to Course 1			
No. of patients treated with second course (n =96)	NR 63	MR 1	PR 28	CR 4
Response to courses 1 and 2				
NR	60	—	—	—
MR	1	—	—	—
PR	2	1	25	—
CR	—	—	3	4
	Response to Courses 1 and 2			
No. of patients treated with third course (n = 38)	NR 9	MR 1	PR 21	CR 7
Response to courses 1-3				
NR	9	—	—	—
MR	—	—	—	—
PR	—	—	13	—
CR	—	1	8	7
	Response to Courses 1-3			
No. of patients treated with fourth course (n = 10)	NR 1		PR 7	CR 2
Response to courses 1-4				
NR	1		—	—
PR	—		5	—
CR	—		2	2

after subsequent courses of IL-2 therapy. All patients who experienced PRs ultimately progressed. The median durations of PR for patients with metastatic melanoma and those with renal cell cancer were 21 and 36 months, respectively. In contrast, patients who achieved CRs had continued, ongoing responses at 21 to 162 months for melanoma and at 36 to 147 months for renal cell cancer. Factors that might predict or be associated with CR among patients treated with high-dose IL-2 have been analyzed previously.[1] Prior immunotherapy adversely affected the chances of achieving a CR. Five of the 28 patients who achieved CRs in this study had received two or more therapies before high-dose IL-2 alone. The median duration of response for this group was 84 months (range, 46 to 147 months). Two or more previous therapies had been given to eight of 33 patients who achieved PRs to high-dose IL-2 alone. The median duration of response for this group was 36 months (range, 8 to 142 months).

Indications for Discontinuing Treatment

In these 350 patients, there were three treatment-related deaths. Table 5 lists the reasons for discontinuing treatment after each of the four courses. The majority of patients developed progressive disease at some point during treatment. Once this occurred, treatment was stopped. Several patients developed severe IL-2 toxicity that was not easily reversed by supportive measures, and these patients were not retreated. These toxicities included mental status changes that required intubation, severe cardiac arrhythmias, and severe renal dysfunction. The cardiopulmonary,[3,6-13] renal,[3,6-9,14-17] and hematologic[3,6-9,18,19] toxicities associated with IL-2 administration have been described in detail.

Table 5. Reasons for Discontinuing Treatment With IL-2 in Patients With Melanoma and Renal Cell Cancer

	No. of Courses Completed Before Discontinuation (no. of patients)			
Reason	1	2	3	4
Progressive disease	176	77	17	6
IL-2 toxicity	8	5	1	1
Death	3			
CR		4	19	1
Other	4	15	6	7

The reasons for discontinuing treatment listed as "Other" in Table 5 included IL-2 intolerance to the reversible non–life-threatening side effects (eg, nausea and diarrhea) and patient refusal. Classified in this category were 32 patients for whom the reason for discontinuation of therapy could not be ascertained from the medical records.

DISCUSSION

The objective response rate of patients with metastatic melanoma or renal cell cancer treated with high-dose bolus IL-2 has been reported in most series to be 15% to 25%, with 5% to 10% of patients achieving CRs.[1] Clinical experience with this regimen over the last decade has led to a reduction in the morbidity associated with this therapy.[3,6] Although our expertise in the administration of IL-2 has improved, there is little information regarding the broader clinical issues concerning when to discontinue therapy for patients with stable metastatic disease. Furthermore, there is no established guideline for how long to continue consecutive courses of therapy for patients who show responses to treatment. This retrospective analysis focused on the tempo of clinical responses to address these issues.

The response rate to IL-2 in the melanoma cohort was 15.4% (10 CRs and 13 PRs). Among these 23 patients, 21 achieved at least PRs after the first course of therapy. The response rate in the renal cell cancer cohort was 19.0% (18 CRs and 20 PRs). Among these 38 patients, 34 achieved at least PRs and one developed an MR after the first course of therapy. Thus, in both histologic cohorts, the preponderance

(90%) of patients who responded to this regimen were identified after one course of therapy.

It is known that, for patients with renal cell cancer or melanoma who respond to high-dose IL-2, CRs are usually durable, whereas patients with PRs eventually progress.[1] Our strategy for patients who developed PRs to IL-2 was to offer additional courses of IL-2 as tolerated, provided that there was evidence of stable or regressing disease. We also gave a consolidation course after a CR was achieved. The outcome of successive courses of therapy for patients with melanoma who developed PRs and then received additional courses of therapy is noted in Table 3. One of the 17 patients with melanoma who had developed PRs to course 1 achieved a CR to course 2 of IL-2, and one of 11 patients with PRs after the second course of therapy achieved a CR after course 3 of IL-2. The outcome for patients with renal cell cancer who developed PRs and then received additional courses of therapy is noted in Table 4. Three of the 28 patients with renal cell cancer who developed PRs to course 1 achieved CRs in course 2 of IL-2, and eight of 21 patients who had PRs after the first and second courses of therapy achieved CRs after course 3 of IL-2. Two of the seven patients with PRs after three courses of therapy achieved CRs after the fourth course of IL-2. Because of the strategy used to determine which patients were retreated, we could not determine whether those patients with PRs would have achieved CRs even if no further treatment had been given.

The outcome for patients who showed no response to IL-2 and subsequently received additional IL-2 was analyzed according to the course of therapy. (Tables 3 and 4). Forty-three patients in the melanoma cohort who had no response to course 1 of IL-2 received a second course of therapy. Among these patients, two achieved PRs after course 2, and with further therapy, one of these individuals ultimately achieved a CR. Sixty-three patients in the renal cell cancer cohort who had no response to course 1 of IL-2 received a second course of therapy. Among these patients, two achieved PRs and one an MR after course 2, and with additional therapy, one of these three attained a CR. There were eight patients in the melanoma cohort and nine in the renal cell cancer cohort who had no response to courses 1 and 2 of IL-2. These patients went on to receive a third course of IL-2. Interestingly, none of these patients responded to therapy.

This study can be helpful in guiding decisions regarding the administration of high-dose bolus IL-2 in patients with metastatic melanoma or renal cell cancer. Patients with evidence of clinical responses should be treated aggressively, being offered treatment courses until there is disease progression or an inability to tolerate IL-2. In our experience, this generally resulted after the administration of two or three courses of therapy. It is encouraging that, with successive courses of IL-2, additional tumor regression could be observed and that some responses could be converted from partial to complete. This was most evident in the renal cell cancer cohort, among whom eight of 21 patients who had achieved PRs after two courses of therapy were classified as having achieved CRs after a third course of IL-2 (Table 4).

Patients with stable disease after the first course of IL-2 therapy should be considered for a second course of therapy. This recommendation is based on the recognition that, although these patients may be less likely to respond to a second course of IL-2, there are few attractive alternative treatments. After two courses of therapy, patients with stable disease are unlikely to respond to additional therapy and should not be retreated. These guidelines apply only to the high-dose bolus IL-2 regimen used in this study. Definitive data concerning the impact of multiple courses of treatment on the incidence of responses can be derived only from prospective studies in which patients are randomized to receive a predetermined number of treatment courses. To our knowledge, no such studies are in progress or planned.

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