Results of Treatment of 255 Patients With Metastatic Renal Cell Carcinoma Who Received High-Dose Recombinant Interleukin-2 Therapy

By Gwendolyn Fyfe, Richard I. Fisher, Steven A. Rosenberg, Mario Sznol, David R. Parkinson, and Arthur C. Louie

Purpose: **To determine the efficacy and toxicity of a high-dose interleukin-2 (IL-2) regimen in patients with metastatic renal cell carcinoma.**

Patients and Methods: **Two hundred fifty-five assessable patients were entered onto seven phase II clinical trials. Proleukin (aldesleukin; Chiron Corp, Emeryville, CA) 600,000 or 720,000 IU/kg was administered by 15-minute intravenous (IV) infusion every 8 hours for up to 14 consecutive doses over 5 days as clinically tolerated with maximum support, including pressors. A second identical cycle of treatment was scheduled following 5 to 9 days of rest, and courses could be repeated every 6 to 12 weeks in stable or responding patients.**

Results: **The overall objective response rate was 14% (90% confidence interval [CI], 10% to 19%), with 12 (5%) complete responses (CRs) and 24 (9%) partial responses (PRs). Responses occurred in all sites of disease, including bone, intact primary tumors, and visceral metastases, and in patients with large tumor burdens or bulky individual lesions. The median response duration for patients who achieved a CR has not been reached, but was 19.0 months for those who achieved a PR. Baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) was the only predictive prognostic factor for response to IL-2. While treatment was associated with severe acute toxicities, these generally reversed rapidly after therapy was completed. However, 4% of patients died of adverse events judged to be possibly or probably treatment-related.**

Conclusion: **High-dose IL-2 appears to benefit some patients with metastatic renal cell carcinoma by producing durable CRs or PRs. Despite severe acute treatment-associated toxicities, IL-2 should be considered for initial therapy of patients with appropriately selected metastatic renal cell carcinoma.**

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THE INCIDENCE of renal cell carcinoma in the United States is approximately 18,000 cases per year and the disease comprises 3% of all adult cases of cancer. The anatomic location and the absence of early symptoms usually prevent early detection.[1] The tumor spreads hematogenously, invades local lymph nodes, and extends locally into surrounding tissues.[2] Up to 57% of patients will present with metastatic disease and more than 90% may eventually develop distant spread.[3] Metastatic disease is associated with a poor prognosis and carries an 80% to 100% 5-year mortality rate.[4] Patients diagnosed with metastatic renal cell carcinoma are resistant to radiotherapy, hormonal therapy, and chemotherapy and have a median survival duration of less than 1 year.[5-14] One biologic agent, interferon-alfa, has consistently produced objective responses in the range of 5% to 27%[15]; however, most responses to interferon-alfa have not been durable.

Interleukin-2 (IL-2) is a biologic agent that, to date, has demonstrated substantial activity in metastatic renal cell carcinoma. IL-2, a T-cell growth factor, was first identified in 1976 and isolation of the cDNA clone was described in 1983.[16] Subsequently, recombinant IL-2 (rIL-2) was shown to have potent antitumor activity in a number of murine tumor models.[17] Based on animal model data, a high-dose IL-2 regimen was developed, administered by short intravenous (IV) infusion every 8 hours, with or without lymphokine-activated killer (LAK) cells. This regimen induced impressive responses in some patients with renal cell carcinoma in the initial clinical trials.[18,19] This regimen and related regimens were subsequently used in several trials to determine the activity of IL-2 in metastatic renal cell carcinoma, metastatic melanoma, and other solid tumors. This report describes results from a recently updated 255-patient data base of all patients treated in phase II studies of high-dose, single-agent IL-2 (Proleukin [aldesleukin], Chiron recombinant IL-2; Chiron Corp, Emeryville, CA) in the treatment of metastatic renal cell carcinoma. The 255 patients were entered onto seven phase II clinical trials conducted at 21 institutions. Participating investigators and study sites are listed in the Appendix. Subgroups of these patients have been described in previous reports.[20-24]

From Chiron Corp, Emeryville, CA; Loyola University Medical Center, Chicago, IL; Surgery Branch and Investigational Drug Branch, National Cancer Institute, Bethesda, MD; and Pro-Neuron, Rockville, MD.

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Address reprint requests to Gwendolyn Fyfe, MD, Chiron Corp, 4560 Horton St, Emeryville, CA 94608-2916.

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PATIENTS AND METHODS

Patient Eligibility

Eligibility criteria varied slightly among studies. In general, patients with histologically confirmed metastatic renal cell carcinoma who were ≥ 16 years of age were eligible to participate in these protocols if they were capable of giving informed consent, had a good performance status (PS; Eastern Cooperative Oncology Group [ECOG] 0 or 1, Karnofsky 70 to 100), and adequate organ function. Adequate organ function was defined as follows: creatinine concentration ≤ 1.5 mg/dL (clearance of 60 mL/μL), normal bilirubin concentration, platelet count ≥ 100,000/μL, and WBC count ≥ 3,500 μL. Patients also had to have adequate pulmonary reserve and be able to receive pressors. Previous hormonal therapy, chemotherapy, or radiation therapy was allowed, provided that at least 4 weeks had elapsed since completion of therapy and complete recovery from treatment-related side effects had occurred. No prior therapy with IL-2 was permitted. More recent trials evaluated cardiac and pulmonary parameters rigorously with formal pulmonary function tests and cardiac treadmill testing to exclude high-risk patients.

Exclusions

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 1 carcinoma of the uterine cervix), organ allografts, corticosteroid dependence, infection with human immunodeficiency virus or hepatitis, or CNS metastases were not eligible in most studies. Patients who were pregnant or nursing were also excluded.

Treatment Plan

IL-2 was administered by 15-minute IV infusion every 8 hours for 14 consecutive doses over 5 days, as tolerated. After a 5- 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. One to two additional courses of treatment could be given to patients who showed evidence of tumor regression or stable disease.

Dosing

IL-2 doses used were 720,000 IU/kg (0.044 mg/kg; two studies) or 600,000 IU/kg (0.037 mg/kg; five studies). Dose modification for toxicity was accomplished by omitting rather than reducing doses. Doses were generally withheld when the following occurred: (1) hypotension that required maximum pressor support; (2) oliguria that was unresponsive to fluid replacement and diuretics; (3) respiratory distress when further diuretics and pressors could not be tolerated; (4) sustained ventricular tachycardia or signs of myocardial ischemia; and (5) neurocortical toxicity manifested as mental confusion. No attempt was made to make up for skipped doses.

Concomitant Medications

Concomitant medications commonly administered included acetaminophen, indomethacin, meperidine, ranitidine or cimetidine, hydroxyzine hydrochloride or diphenhydramine, dopamine, phenylephrine hydrochloride, diuretics, antibiotics, antiemetics, antidiarrheal medications, and sedatives. Dexamethasone was permitted for patients with grade 4 life-threatening adverse events unresponsive to other measures.

Adverse Event Gradations

The National Cancer Institute (NCI) 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. The reversibility of adverse events was evaluated by analyzing time to hospital discharge following the first course of therapy.

Response Criteria/Definitions

Radiographs of responding patients were centrally reviewed. All bidimensionally measurable lesions were serially evaluated and a total tumor burden calculated. Criteria to assess complete responses (CRs) and partial responses (PRs) were based on those reported by Oken et al.[25] A CR was defined as the complete disappearance of tumor, including symptoms and laboratory abnormalities associated with tumor, documented on at least two occasions ≥ 28 days apart. A PR was defined as a 50% or greater reduction in measurable tumor area (sum of the 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 ≥ 28 days apart. Response duration was calculated from the initial documentation of best response to the time of progression, last follow-up evaluation, or death. Survival was calculated from the first dose of IL-2 to the time of death or last follow-up evaluation. Progression-free survival was calculated for responding patients only and was calculated from the first dose of IL-2 to the time of progression, last documented clinical visit, or death.

Multivariate Analyses

Multivariate analyses of demographic and clinical factors were performed in an attempt to determine prognostic factors predictive of response and survival. Factors examined included PS, number of organs involved with metastatic disease, time from diagnosis of renal cell carcinoma to treatment, and presence or absence of prior chemotherapy. Other factors examined were age, presence or absence of prior nephrectomy, and presence of metastatic disease limited to the lung.

RESULTS

Demographics

The characteristics of the 255 patients are listed in Table 1. Patient characteristics were similar in all seven studies (data not shown). The median patient age was 52 years (range, 18 to 71), and there were 178 men (70%) and 77 women (30%). Study patients had an excellent or good PS, with 166 patients (65%) with PS 0, 80 (31%) with PS 1, and nine (4%) with PS ≥ 2. The median time from diagnosis of renal cell carcinoma to treatment with IL-2 was 8.5 months. Prior nephrectomy was reported in 85% of patients, but prior chemotherapy was uncommon (3%).

Table 1. Demographic Summary: All Patients

Characteristic	No.	%
No. of patients	255	
Age (years)		
Median	52	
Range	18-71	
Sex		
Female	77	30
Male	178	70
ECOG PS		
0	166	65
1	80	31
2	8	3
3	0	0
4	1	1
Time from diagnosis to first IL-2 dose (months)		
Median	8.5	
Range	0-365.6	
No. ≤ 1 year	143	56
No. > 1 year	112	44
Prior therapy		
Nephrectomy	218	85
Chemotherapy	8	3

Dosing

Sixty-eight patients received 720,000 IU/kg IL-2 every 8 hours (two studies) and 187 patients received 600,000 IU/kg every 8 hours (five studies). IL-2 was administered every 8 hours until dose-limiting toxicity was encountered, at which time doses were omitted until toxicities resolved to an acceptable level. The protocol specified a maximum of 28 doses per course of therapy, although most patients received fewer doses. In practice, the median cumulative dose per course of therapy was the same, since the 720,000-IU/kg regimen delivered a median of 15 doses per course, while the 600,000-IU/kg regimen delivered a median of 20 doses per course. The median cumulative doses administered were 10.6 (range, 3.6 to 16.3) $\times$ 10^6 IU/kg and 11.6 (range, 1.2 to 22.2) $\times$ 10^6 IU/kg for the 720,000- and 600,000-IU/kg doses, respectively. The response rate for the two regimens was the same, and there was no apparent relationship between cumulative dosing and probability of response. Only 20% of nonresponding patients received more than one course of treatment.

Efficacy

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. The total response rate for the 255 patient population was 14% (95% confidence interval [CI], 10% to 19%). There were 12 (5%) CRs and 24 (9%) PRs (Table 2).

Responses were noted in the lung, liver, lymph nodes, spleen, adrenal, mediastinum, bone, and other sites. Responses were also noted in patients with intact renal primary lesions and large renal-bed recurrences. Tumor response data and characteristics of the 36 responding patients are listed in Tables 3 and 4.

The median duration of response for all responders is 20.3 months. Kaplan-Meier analyses project that 78% and 55% of responding patients will remain in response for 12 and 18 months, respectively (Fig 1). The median response duration for patients who achieved a CR has not been reached, with eight of the 12 CRs ongoing at 62+, 61+, 46+, 35+, 25+, 8+, 6+, and 5+ months. Four patients with a CR had progressive disease at 17, 16, 11, and 7 months (Fig 1).

The median duration of PRs is 19.0 months. For PR patients, 77% are projected to remain in response at 12 months and 54% at 18 months (Kaplan-Meier). Of these patients, three had surgical resection of residual disease while still in remission at 3, 5, and 6 months. Although they remain free of disease at last follow-up evaluation, their response durations were censored at the time of surgery. In all, 16 of 21 remaining PRs lasted ≥ 12 months (Fig 1). Twelve of 24 PR patients had greater than 90% regression of their overall disease, and three of these patients had less than 1 cm^2 of residual tumor at the time of maximal response.

Predictors of response were identified using a Cox multivariate regression analysis of factors that have been predictive of survival in other studies (Table 5). Baseline ECOG PS was the only prognostic factor predictive of response ($P = .03$), with patients with PS 0 having twice the rate of objective responses (17% *v* 9%) as patients with PS 1. In addition, the PS 0 group had 11 of the 12 CRs. Although patients with a PS greater than 0 were less likely to respond, the duration of response was not different from those with a PS of 0. The interval from

Table 2. Summary of Efficacy

	Response Rate		Response Duration (months)	
Response	No.	%	Median	Range†
CR	12	5	NR	5+-62+
PR*	24	9	19	3-57+
PR + CR	36	14	20.3	3-62+

Abbreviation: NR, not yet reached.

*Three partial responders had surgery while in PR and remain disease-free. Duration of response censored from date of surgery.

†Plus signs mean ongoing.

Table 3. Characteristics of Responding Patients: Complete Responders

Patient No.	EGOG PS/ Nephrectomy	Baseline Measurable Tumor (cm^2)	% Regression	Response Duration (months)	Sites of Tumor Regression
197	0/yes	5.3	100	61+	Lung
198	0/yes	13.4	100	62+	Lung
191	0/yes	35.9	100	17	Lung (paravertrebral mass), paraaortic node
205	0/yes	54.9	100	46+	Lung, lymph node
001	0/yes	10.6	100	35+	Lung
1	0/yes	18.8	100	25+	Lymph node, mediastinum
4438	0/yes	21.5	100	16	Lymph node
055621471	0/yes	42.5	100	8+	Lung, mediastinum (periaortic)
2381291	0/yes	17.7	100	6+	Lung
2376155	0/yes	40.4	100	7	Lung (prevascular), mediastinum (paratracheal, subcarinal)
061166518	0/yes	106.5	100	11	Mesenteric mass, muscle, liver
1509376	0/yes	14.8	100	5+	Lung, mediastinum

diagnosis to treatment (which may represent an index of the pace of the disease) and the number of sites of metastatic disease or disease limited to the lung were not correlated with or predictive of response.

Tumor burden was defined as the sum of the areas of all measurable lesions. Figure 2 shows the distribution of tumor burden for responding patients. Fourteen of the responding patients (38%) began treatment with tumor burdens $\geq$ 50 cm^2; two of these 14 achieved CRs and eight others had PRs with greater than 90% tumor regression. Durable CRs and PRs were also achieved in patients with large individual lesions. Bulky lesions were defined as those $\geq$ 25 cm^2. One third of 36 responding patients had individual tumor masses larger than 25 cm^2, with the largest single lesion being an 11- $\times$ 12-cm renal-bed mass (Table 6). Seven of these 12 patients, identified in Table 6

Table 4. Characteristics of Responding Patients: Partial Responders

Patient No.	ECOG PS/ Nephrectomy	Baseline Measurable Tumor (cm^2)	% Regression	Response Duration (months)	Sites of Tumor Regression
194	0/yes	2.7	81	7	Lung
194*	1/yes	17.1	95	28	Lung, adrenal
196	0/yes	8.1	52	16	Lung, bone, lymph node
203	0/yes	42.6	96	57+	Lung, lymph node
201	0/yes	81.1	96	18	Lung
199	0/yes	22.4	66	25	Lung, mediastinum
659	1/yes	64.0	93	31	Lung, paraaortic and paracaval, retroperitoneal mass
093	0/yes	302.8	92	8	Lung
009	1/yes	43.9	73	4	Renal, lung (hilar adenopathy)
2309269*	0/yes	14.9	$\geq$ 99	16	Lung
1479558	1/yes	35.3	88	13	Renal, lung, lymph node
2310053	0/yes	24.2	83	22+	Lung, renal bed
105249278	0/yes	6.4	64	3	Lung, lymph node
1478098	0/yes	66.8	73	20+	Lung
017	1/yes	59.4	97	20+	Lymph node, pelvic mass
371	0/yes	67.4	95	20	Lung, muscle
116655977	0/yes	51.1	88	16+	Lung, renal bed
019	0/yes	22.9	94	19+	Lung
018	0/yes	174.7	93	8	Renal, adrenal, liver, spleen, lymph node
012	0/yes	65.6	98	12+	Lung, mediastinum (aortic, pericardiac), retrocrural lymph node
3*	0/yes	98.1	$\geq$ 99	13+	Lung
773†	0/yes	137.7	75	5+	Lung, renal, lymph node
001†	0/yes	48.0	83	6+	Pelvic mass
010†	1/yes	168.2	77	3+	Kidney, lymph node, lung, adrenal, perinephric

*Patients had $<$ 1 cm^2 residual tumor at the time of maximal response.

†Surgical resection of all residual disease was performed while the patient was in PR; response duration censored from the date of surgery. These patients remain alive and without disease progression up to the time of last follow-up evaluation.

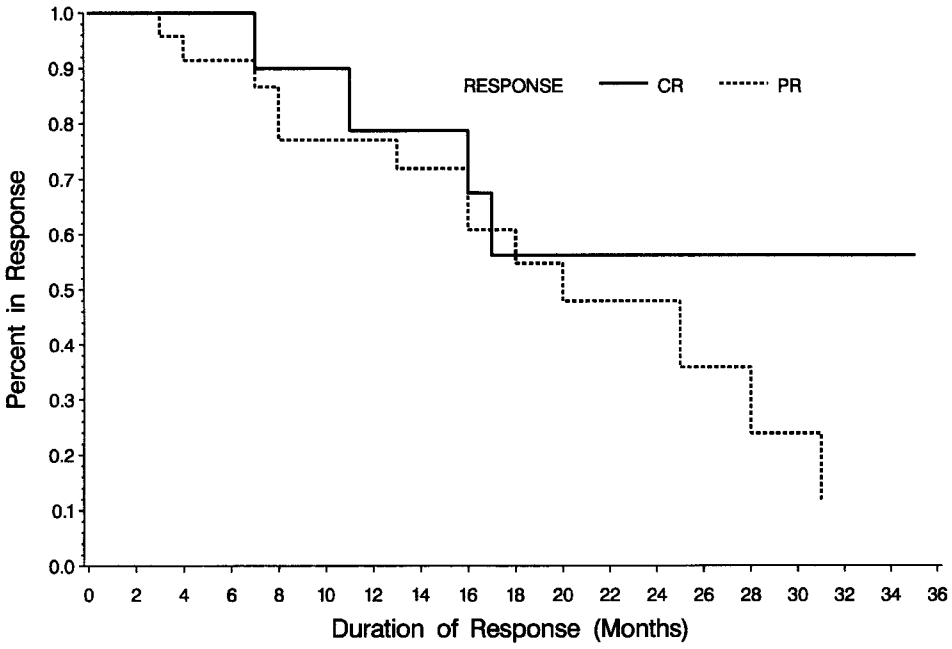

Fig 1. Response durations in all responders. P, best response = PR; C, best response = CR.

by an asterisk, had complete disappearance of their bulky lesion.

The median survival duration (Kaplan-Meier) for the entire 255-patient data base is 16.3 months. The rigorous patient entry criteria for high-dose IL-2 regimens do not allow direct comparisons to other treatment data bases, but, given the median survival time of less than 1 year in most series of patients with metastatic renal cell carcinoma, IL-2 therapy is unlikely to have decreased the median survival duration of the group as a whole. The median survival duration for responding patients cannot be calculated, because only three of 36 responding patients have died.

Using a Cox multivariate analysis, three prognostic factors predicted for improved survival in this data base. The most important predictors of survival were ECOG PS ($P < .01$), prior nephrectomy ($P < .01$), and time from diagnosis to treatment when analyzed as a continuous variable ($P = .01$). Also, age almost reached statistical significance ($P = .06$).

Table 5. Subset Analysis: Response

Prognostic Factor	P
ECOG PS	.03
Organ sites	.69
Time from diagnosis to treatment ≤ 1 year v > 1 year	.51
Prior chemotherapy	.89
Age	.28
Prior nephrectomy	.12
Disease limited to lung	.29
Time from diagnosis to treatment: continuous	.99

Toxicity

The toxicity data base for the 255 patients presented here represents a cumulative experience spanning a period of almost 5 years. During this period, both patient selection processes and the standard of care for IL-2–treated patients on this regimen changed substantially.

Eleven (4%) of 255 patients died of treatment-related toxicity during the trial. Six of the 11 patients entered the trial with a PS of 0 and five with a PS of 1. Most deaths were the result of multiple medical complications. Toxicities associated with the capillary leak syndrome (CLS), including myocardial infarctions and respiratory failure, led to the deaths of six patients. Gastrointestinal toxicities contributed to the deaths of three patients. Sepsis or pneumonia also contributed to the deaths of two of these patients and was the primary cause of death in one other patient. One patient died at home of an unknown cause almost 2 weeks following hospital discharge.

Most of the severe toxicities observed during intensive IL-2 therapy were associated with CLS and resembled the clinical manifestations of septic shock. Hypotension was the most common toxicity and occurred in 96% of patients, with grade 4 hypotension reported in 15%. Arrhythmias were reported in 14% of patients, but life-

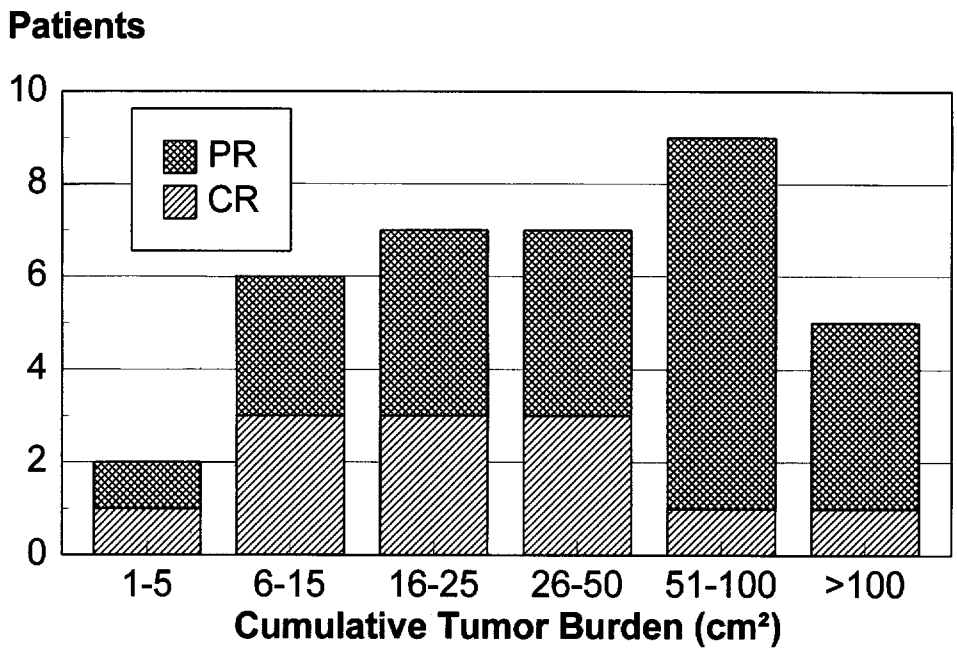

Fig 2. Tumor burden and response.

threatening ventricular tachycardias occurred in less than 1%. Myocarditis was reported in 1% of patients and myocardial infarction in 2%. Grade 4 respiratory events, including dyspnea, adult respiratory distress syndrome, and respiratory failure occurred in 4%. Nausea, vomiting, and diarrhea were common, but life-threatening gastrointestinal side effects were rare (gastrointestinal bleeding rate, 1%; perforation rate, < 1%). Mental status changes were also common and could be severe; grade 4 mental status changes, including some patients with coma, occurred in 7%. Elevations of blood urea nitrogen and creatinine levels were common and could be dose-limiting; however, all patients recovered renal function following completion of therapy. Grade 4 increases in bilirubin and transaminase levels were observed in 11% of patients, but these abnormalities were not considered dose-limiting and did not lead to chronic liver dysfunction. Sepsis was also observed and contributed to toxicity in some patients; life-threatening sepsis occurred in 2% of patients. Thyroid dysfunction was observed in this series, possibly as a result of an autoimmune response.[26-32] Some patients required temporary thyroid replacement therapy, but most had return of normal thyroid function following treatment. Toxicities are listed by organ system in Table 7.

Table 6. Response in Patients With Bulky Disease (≥ 25 cm²)

Patient No.	Largest Lesion Size (cm)	Site	Response Duration (months)
773	11 × 12	Renal bed	PR 5+
18	9 × 9*	Renal bed	PR 8
06116658	9 × 7*	Psoas muscle	CR 11
010	6.5 × 8.5	Periphrenic mass	PR 3+
017	8.5 × 6.2*	Pelvic mass	PR 20+
001	6 × 8	Pelvic mass	PR 6+
371	8 × 4.5*	Lung	PR 20
203	6 × 5.6	Lung	PR 57+
659	8 × 4	Paraaortic mass	PR 31
205	5.2 × 5.3*	Hilum	CR 46+
3	5 × 7*	Hilum	PR 13+
12	5 × 5*	Hilum	PR 12+

*Single largest lesion completely disappeared.

The rapidity of recovery from acute treatment toxicities can be measured by calculating the time to hospital discharge following the last dose of IL-2 treatment. Despite toxicities that required management in the intensive care unit, the median time to discharge after the first course of treatment was 3 days and, by 7 days, 89% of patients had been discharged. Infectious complications were the most common cause of delayed discharge.

The incidence of severe toxicities in patients with PS 0 versus PS 1 was analyzed separately. When compared with patients with PS 1, patients with PS 0 appeared to have fewer grade 4 mental status changes (4% *v* 9%), coma (1% *v* 4%), grade 3 or 4 respiratory events (14% *v* 24%), grade 3 or 4 gastrointestinal bleeding (3% *v* 6%), and hospital discharge delays beyond 1 week (8% *v* 24%).

DISCUSSION

The treatment of metastatic renal cell carcinoma has included hormonal therapy, radiotherapy, single-agent or aggressive combination chemotherapy regimens, and, more recently, biologic agents such as interferon alfa. Although response rates of 15% to 20% have been reported with these agents in some single-institution trials, few durable responses have been documented and no agent has been considered effective treatment for metastatic disease.

Table 7. Incidence of Most Common and Most Severe Adverse Events (N = 255)

Event by Body System	Grade (%)		
	All	3	4
Cardiovascular			
Hypotension	96	59	15
Arrhythmias	14	2	0
Supraventricular	5	2	1
Ventricular	1	0	0
Myocardial ischemia	2	1	<1
Myocardial infarction	2	0	2
Cardiac arrest	2	<1	2
Myocarditis	1	1	0
Gastrointestinal			
Nausea and vomiting	89	24	1
Diarrhea	81	20	2
Stomatitis	32	4	0
Gastrointestinal bleeding	15	3	1
Intestinal perforation	1	0	<1
Neurologic			
Mental status changes	82	23	5
Coma	2	0	2
Seizure (grand mal)	2	1	1
Pulmonary			
Dyspnea	57	16	1
Adult respiratory distress syndrome	1	<1	<1
Respiratory failure	3	<1	2
Hepatic			
Elevated bilirubin level	85	13	8
Elevated transaminase level	72	7	3
Elevated alkaline phosphatase level	77	8	<1
Renal			
Acidosis	19	4	2
Elevated BUN level	85	12	2
Oliguria/anuria	81	40	6
Serum creatinine elevation	81	11	3
General			
Fever and/or chills	97	19	5
Asthenia	39	4	0
Edema	55	2	0
Sepsis	8	4	2
Hematologic			
Thrombocytopenia	83	16	5
Anemia	99	15	3
Other			
Pruritus	53	4	0
Rash	25	1	0
Arthralgia	7	1	0
Myalgia	7	1	0

Abbreviation: BUN, blood urea nitrogen.

High-dose IL-2 produced a modest response rate in this series of 255 patients treated at 21 institutions. Unlike other agents with low response rates in metastatic renal carcinoma, responses that occurred as a result of IL-2 treatment were durable. The median duration for CRs in this series of patients has not been reached, and the median duration for PRs is 19 months, with many of the responses still ongoing. The clinical responses in this trial were also unusual because they were not limited to patients with exclusively good-risk features. In the regression analysis for response, there was no correlation of response with number of involved organ sites or disease limited to the lung. Patients with large tumor burdens or bulky disease responded to therapy. Responses occurred in patients with bone disease, intact primary tumors, and multiple sites of visceral disease. Response was not correlated with a long interval from diagnosis until treatment, as is often noted in the long-lived nonresponders in other series.

High-dose IL-2 in this series resulted in an on-study death rate of 4%, and other patients experienced significant reversible morbidity. However, most severe toxicities were rapidly reversible, as documented by the median hospital discharge of 3 days following completion of treatment. Many severe IL-2 toxicities are related to CLS. While the pathogenesis of CLS is still not completely understood, the clinical spectrum of IL-2 toxicities is well described.[33] Over the 5 years encompassed in this series, much has been learned about appropriate patient selection and management.[34,35] For example, routine screening with exercise or thallium stress testing and pulmonary function testing has led to the exclusion of higher-risk patients with preexisting cardiopulmonary disease. The importance of selecting patients with a good PS has also become apparent, since PS is predictive of response and may be predictive of tolerance to treatment.

Techniques of patient management have also evolved. Antibiotic prophylaxis for patients with indwelling lines became routine in 1989 and has resulted in a reduced incidence of line sepsis.[36-38] Supportive care and use of concomitant medications has improved over the course of these seven clinical trials. The use of low-dose dopamine early in the course of therapy for the treatment of oliguria and the sparing use of fluids

have been recommended.[34] These measures probably decrease the incidence of serious complications related to IL-2 therapy.

High-dose IL-2 treatment for patients with metastatic renal cell carcinoma has been shown to lead to durable PRs and CRs. In the 10 years that IL-2 has been studied in patients with metastatic renal cell carcinoma, a great deal has been learned about the mechanisms of efficacy and toxicity associated with high-dose IL-2 therapy, but more knowledge is necessary. At this time, IL-2 is being investigated both as a high-dose agent administered with other drugs to ameliorate severe toxicities and also in less toxic regimens to determine if comparable efficacy can be demonstrated. The optimal IL-2 regimen for achieving durable objective responses without severe toxicities has yet to be defined.

APPENDIX
Participating Investigators

Jeffrey Abrams, MD, University of Maryland Cancer Center, Baltimore, MD
Fred Aronson, MD, University of California, San Francisco, San Francisco, CA
Michael Atkins, MD, New England Medical Center, Boston, MA
Jeffrey Clark, MD, Roger Williams Hospital, Providence, RI
Edward Crum, MD, Case Western Reserve University, Cleveland, OH
Jan Dutcher, MD, Albert Einstein Cancer Center/Montefiore Hospital, Bronx, NY
David Ettinger, MD, Johns Hopkins University, Baltimore, MD
Richard I. Fisher, MD, Loyola University Medical Center, Maywood, IL
Jonathan Fleischman, MD, Metro Health Medical Center, Cleveland, OH
John Glick, MD, University of Pennsylvania, Philadelphia, PA
Michael J. Hawkins, MD, National Cancer Institute, Investigational Drug Branch, Bethesda, MD
Benjamin Kim, MD, Case Western Reserve University, Cleveland, OH
Robert Krigel, MD, Fox Chase Cancer Center, Philadelphia, PA
Rene Lafreniere, MD, University of Calgary, Calgary, Canada
Kim Margolin, City of Hope Hospital, Duarte, CA
Howard Ozer, MD, University of North Carolina, Chapel Hill, NC
David R. Parkinson, MD, New England Medical Center/Tufts University, Boston, MA
Anthony Rayner, MD, University of California, San Francisco, San Francisco, CA
Bruce Redman, DO, Wayne State University, Detroit, MI
Steven A. Rosenberg, MD, Surgery Branch, National Cancer Institute, Bethesda, MD
Wolfram Samlowski, MD, University of Utah, Salt Lake City, UT
James Stewart, MD, University of Vermont, Burlington, VT
Mario Sznol, MD, National Cancer Institute, Investigational Drug Branch, Bethesda, MD
Mary Todd, DO, Yale University School of Medicine, New Haven, CT
Nicholas Vogelzang, MD, University of Chicago, Chicago, IL
Geoffrey Weiss, MD, University of Texas, San Antonio, TX
Peter Wiernik, MD, Albert Einstein Medical Center/Montefiore Hospital, Bronx, NY
James Yang, Surgery Branch, National Cancer Institute, Bethesda, MD

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