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Randomized Study of High - Dose and Low - Dose Inter leukin - 2 in Patients With Metastatic Renal Cancer

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Abstract

Purpose—This three-arm randomized study compares response rates and overall survival of patients with metastatic renal cell cancer (RCC) receiving high-dose or one of two low-dose interleukin-2 (IL-2) regimens.

Patients and Methods—Patients with measurable meta-static RCC and a good performance status were randomized to receive either 720,000 U/kg (high-dose [HD]) or 72,000 U/kg (low-dose [LD]), both given by intravenous (IV) bolus every 8 hours. After randomly assigning 117 patients, a third arm of low-dose daily subcutaneous IL-2 was added, and an additional 283 patients were randomly assigned.

Results—A total of 156 patients were randomly assigned to HD IV IL-2, and 150 patients to LD IV IL-2. Toxicities were less frequent with LD IV IL-2 (especially hypotension), but there were no IL-2-related deaths in any arm. There was a higher response proportion with HD IV IL-2 (21%) versus LD IV IL-2 (13%; $P = .048$) but no overall survival difference. The response rate of subcutaneous IL-2 (10%, partial response and complete response) was similar to that of LD IV IL-2, differing from HD IV ($P = .033$). Response durability and survival in completely responding patients was superior with HD IV compared with LD IV therapy ($P = .04$).

Conclusion—Major tumor regressions, as well as complete responses, were seen with all regimens tested. IL-2 was more clinically active at maximal doses, although this did not produce an overall survival benefit. The immunological factors which constrain the curative potential of IL-2 to only a small percentage of patients need to be further elucidated.

The immunostimulatory cytokine interleukin-2 (IL-2) was first given, along with lymphokine activated killer cells, to patients with advanced cancer in the early 1980s.[1,2] At that time, it was dose-escalated to the maximum-tolerated dose using an every 8 hour schedule based on serum half-life data. Since then, it has become clear that the in vivo bioactivities of IL-2 and the secondary effects that it manifests through tissue immune effector cells are more complicated than can be modeled by simple serum pharmacokinetics. It is also apparent that, for certain tumor types, IL-2 has curative potential in a small subpopulation of patients with metastatic disease. In selected patients with metastatic melanoma and clear-cell renal cancer, the complete response rate to high-dose intravenous (IV) bolus IL-2 is between 5% and 9%, and the majority of these completely responding patients will not relapse according to follow-up data extending to 17 years.[3,4] Based on these data, the United States Food and Drug Administration (FDA) specifically approved the high-dose IV bolus regimen of IL-2 for

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metastatic renal cancer and melanoma. IL-2 remains the only FDA-approved drug for the treatment of metastatic renal cancer and the only cytokine approved for the treatment of metastatic melanoma. In the initial experience with the recommended regimen of IL-2, some investigators encountered significant multisystem toxicity resulting in treatment-related mortalities of 1% to 4%.[5] This led to experimentation with lower dose regimens (often with interferon-alfa), with daily subcutaneous self-administration widely used for convenience and toxicity considerations.[6–10] Small phase II reports of these regimens claimed response rates similar to high-dose bolus IL-2 in patients with metastatic renal cancer (but interestingly, not for patients with metastatic melanoma) and outpatient, subcutaneous or low-dose IV IL-2 was widely adopted with or without interferon-alfa.[11,12] Despite some reservations about the durability of the responses seen with low-dose IL-2 and combinations of IL-2 and other agents,[13] these regimens were not subjected to randomized evaluation before adoption.

Selecting a dose that resulted in a consistent and clinically-evident reduction in IL-2 toxicity was key to designing a study to evaluate the risk-benefit relationship in IL-2 dosing. Based on previous dose-escalation data, it was clear that reductions of even 67% (to 216,000 U/kg) did not avoid multisystem toxicity and hypotension requiring pressors and intensive care unit support. Instead, it was necessary to reduce the dose (given every 8 hours) by 90% to achieve these objectives. Therefore, a randomized trial was begun to compare a low-dose IV regimen utilizing 72,000 U/kg with the high-dose regimen (720,000 U/kg), given at the same intervals and by the same route of administration, to specifically address the issue of whether IL-2 dose was important in response rates and survival of patients with metastatic renal cancer.

Eventually, the widespread use of daily subcutaneous, self-administered IL-2 for renal cancer led to the need for testing such a regimen against high-dose bolus IV IL-2. A representative regimen was published in 1992 by Sleijfer et al,[9] which reported very modest toxicities and a response rate of 23% in 26 patients. This was adopted when the present trial was expanded to three randomized treatment arms, but only concurrently randomized patients were compared in the analyses of the two and three arms. Preliminary data on this trial were published in 1997 in the midst of accrual and with limited follow-up, in order to report the early results of the new low-dose IV regimen.[14,15] We now present the definitive results of this trial with the full accrual of 400 patients, all with active therapy completed and a median follow-up of 7.4 years.

PATIENTS AND METHODS

All patients in this trial had histologically confirmed renal cancer and measurable, metastatic disease with no previous IL-2 therapy and no therapy within the month before randomization. Eligibility was confined to clear-cell renal cancer and standard histology was used to exclude renal tumors of the papillary, medullary, collecting duct, chromophobe, and oncocytic types.[16] There was no exclusion of the granular or sarcomatoid subtypes of clear-cell renal cancer, nor clear-cell tumors with some papillary features. Patients were not eligible if they had an Eastern Cooperative Oncology Group performance status greater than 1, any history of CNS involvement, any recent corticosteroid administration or active autoimmune disease. Coronary artery disease was excluded by history and stress thallium evaluations for all patients older than 50 years. Patients with significant pulmonary, renal, or hepatic insufficiency were also excluded.

Between 1991 and 1993, patients were stratified for the presence or absence of a primary renal tumor and then randomized to receive either high-dose IV IL-2 at 720,000 U/kg every 8 hours to the maximum number of tolerated doses (not to exceed 15 consecutive doses in any one cycle) or 72,000 U/kg IV with the same schedule and dose limit. In 1993, the third treatment arm was added and all subsequent patients were assigned in a balanced, three-way randomization (using the same stratification) to receive one of the two IV therapies, or daily

subcutaneous IL-2, 5 days a week (typically Monday through Friday), beginning at 250,000 U/kg/dose in the first week and then 125,000 U/kg/dose during the next 5 weeks. In both analyses of results, only concurrently randomized patients were considered. All treatments were divided into two month-long courses, with each IV treatment course consisting of two cycles of therapy as described above, separated by approximately 7 to 10 days of rest with no other therapy during the remainder of the 2 months. Patients receiving subcutaneous therapy were allowed 2 weeks of recovery following each 6 weeks of therapy. Patients were assessed by radiological evaluation or physical measurement of all sites of disease every 2 months and were retreated with another 2-month course of IL-2 if stable or regressing. Therapy was stopped, and patients observed if they had two consecutive posttreatment assessments that were unchanged (thus patients showing disappearance of all tumor received one consolidation course of therapy). Following the completion of therapy, patients were assessed every 2 to 4 months for approximately 2 years, and then at increasing intervals thereafter.

A partial response was defined as a ≥ 50% reduction in the sum of the products of maximal perpendicular diameters of all measurable lesions (lasting at least 1 month), with no growth of any preexisting lesion or appearance of a new lesion. A complete response was defined as the complete disappearance of all evidence of metastatic disease for at least a month. Responses were confirmed by at least two investigators. Primary tumors (which in our experience do not regress even in responding patients) were not permitted to increase in any responding patient, but were not otherwise considered in the determination of response. Responding patients with their (stable) primary tumors in place typically underwent completion nephrectomy at a later date. Local recurrences and retroperitoneal nodal involvement were included in response assessments. Durations of partial and complete responses were measured from the time of randomization.

Toxicities of IV IL-2 were managed according to previously published algorithms,[17] with the primary interventions directed at the vasodilatation, oliguria and hypotension seen with IL-2. Initially, up to 1.5 to 2 L of crystalloid were administered within a 24-hour period (in addition to appropriate baseline maintenance fluids) to address these problems, with IV vasopressor support with dopamine and neosynephrine added for failure to respond to fluids. IL-2 doses were only administered if surveillance laboratory values, vital signs and urine output were acceptable and the requirements for fluids and pressors were considered safe and effective.

This study was ultimately designed to accrue a total of 400 patients, and this was achieved. Initially, 88 patients per arm were required in the two-arm comparison of high- and low-dose IV IL-2 in order to detect a difference in response rate of 5% versus 20%, with a two-tailed *P* value of .05 with a power of .80. After the addition of the third arm, taking place after the first 117 patients had been randomly assigned, a minimum of 88 concurrently randomized patients in each of the three arms was again targeted. The accrual ceiling was set at 400 patients, to allow for a small number of additional patients. Because eligibility criteria and treatment methods were held consistent between the two phases of this trial, all patients randomly assigned to either high-dose or low-dose IV therapy were analyzed in the two-arm comparison. The objective of the three-arm study was to compare each low-dose, experimental treatment arm with the FDA-approved standard high-dose IV therapy, so comparisons are pair-wise versus high-dose therapy only and the *P* values presented are unadjusted (but should be interpreted in the context of the two planned comparisons). The difference in response rates was assessed by the χ^2 and Fisher's exact tests, the survival data evaluated with the technique of Kaplan and Meier, and their significance determined using the Mantel-Haenszel method. *P* values are two-tailed.

Prognostic factors associated with clinical response were evaluated on each arm of the study individually (grouped as all high-dose; all low-dose; and subcutaneous). The statistical

significance of dichotomous parameters was determined using Fisher's exact test, while that of continuously measured parameters was determined by the Wilcoxon rank sum test. An evaluation of factors associated with survival greater than 4 years was done after determining, retrospectively, that this appeared to be an important distinction between those who were potentially cured and those who continued to die from their disease. All surviving patients who had been in follow-up for less than 4 years were excluded from analysis. This retrospective evaluation should be interpreted as hypothesis-generating rather than definitive.

This trial was reviewed and approved by the investigational review board of the National Cancer Institute and was subjected to several interim audits by an independent company, THERADEX Corp (Princeton, NJ), in compliance with the standard policies of the intramural program of the National Cancer Institute.

RESULTS

Between 1991 and 2001, a total of 156 patients were randomly assigned to receive high-dose IV bolus IL-2, and 150 patients to low-dose IV bolus IL-2. Table 1 presents the distribution of randomization. Between 1993 and 2001, there was a three-arm comparison of patients concurrently randomized to receive high-dose IV (N = 96), low-dose IV (N = 93), or subcutaneous IL-2 (N = 94). A total of three protocol violations occurred. Two patients had ineligible histologic characteristics determined subsequent to their protocol participation (one patient with lymphoma was randomly assigned to high-dose IL-2 and had a partial response, and one with Ewing's sarcoma to the bone and kidney did not respond to low-dose IL-2) and are evaluated for toxicity but excluded in outcome analyses. One patient given subcutaneous IL-2 had a mixed regression of lung lesions beginning before commencing IL-2 and is considered not assessable for response. Three randomized patients failed to receive any IL-2 (two randomly assigned to high-dose and one to subcutaneous IL-2) but are included in the outcome analysis that was done on an intent-to-treat basis.

Separate analyses were done for the two-arm comparison of patients randomly assigned to receive high- versus low-dose IV IL-2 and the three-arm comparison of high-dose IV, low-dose IV, and subcutaneous IL-2. Within each of the IV regimens, there were no significant differences in demographic parameters, toxicities or response rates of patients in the two-arm versus three-arm phases of this study (data not shown), indicating consistent patient selection and treatment throughout the study. Demographic data for all patients in this study are shown in Table 1. There were no imbalances in clinically significant parameters between arms. Overall, the population of patients had a good performance status and most had their primary tumors resected. The details of therapy for all patients in all arms are presented in Table 1. Although the toxicity of the low-dose IV regimen proved to be low, the dose was not trivial, as more than half of the treatment courses were stopped before the maximum allowable number of doses was administered. There was a clinical policy to try to avoid vasopressor use and intensive care unit support in this treatment arm, in accordance with the intention of administering a therapy with reduced toxicity. This policy and patient refusal were the predominant reasons for stopping prematurely. On the other hand, the majority of patients were able to receive all intended doses on the subcutaneous therapy arm.

Toxicity was markedly reduced when low-dose instead of high-dose IL-2 was given, particularly in the areas of hypotension, disorientation or confusion, and thrombocytopenia (Table 2). With the more protracted course for low-dose IL-2, there was more fatigue and edema. All toxicities in all arms were reversible except for one case of grade-2 neuropathy occurring on low-dose IV IL-2. There was no treatment-related mortality in any arm.

In the two-arm comparison of high-dose versus low-dose IV IL-2 there were 11 complete responses (7%) and 22 partial responses (14%) to high-dose therapy, and for low-dose therapy, there were six complete responses (4%) and 13 partial responses (9%; for overall response rate, $P = .048$ by χ^2 test, and $P = .067$ by Fisher's exact test; Table 3). For the three-arm comparison, the response rates for high-dose IV, low-dose IV, and subcutaneous IL-2 were 21% (6 complete response [CR] and 14 partial response [PR]), 11% (1 CR and 9 PR) and 10% (2 CR and 7 PR), respectively (Table 3). The difference in objective response rates between high-dose IV therapy and subcutaneous therapy was of borderline statistical significance ($P = .033$ by χ^2 test; $P = .043$ by Fisher's exact test). Twenty-seven of 400 evaluable patients underwent therapy with their primary tumors in place; only one patient would change response status (from complete response to no response) if primary tumors were included in measurements. He had complete regression of all metastatic disease (contralateral kidney and multiple lung metastases) following high-dose therapy, but showed no change in his primary tumor, which was later resected.

Response durations (Table 4) indicated a trend toward more complete and durable responses with high-dose IV IL-2 as well. Eight of the 11 patients who had complete tumor regression with high-dose IL-2 remain in ongoing complete response at a median potential follow-up of 9.3 years, two had limited recurrences, were resected and are currently free of disease, and one has died of a relapse of his renal cancer. Of the six patients completely responding to low-dose IV IL-2, three are disease free and three have relapsed and died of renal cancer (median potential follow-up of these patients is 10.1 years). With a median potential follow-up of 7.4 years for all study patients, and 21% of patients surviving at last follow-up, there were no significant differences in overall survival (Fig 1A and B). However, the survival of patients completely responding to high- and low-dose IV IL-2 differs significantly ($P = .04$; Fig 2).

Preliminary investigations of factors associated with an increased probability of response to IL-2 or long-term survival were conducted to identify parameters to aid in the design of future studies and to develop hypotheses concerning the mechanisms of IL-2 mediated tumor regression (Table 5). Only patients who actually received IL-2 for clear-cell renal cancer were included in these analyses. Parameters were evaluated for an association with the probability of a response to therapy or with survival 4 years after randomization (selected based on overall survival curves which demonstrated stabilization of survival at approximately 4 years, and which excluded surviving patients with < 4 years of follow-up). For patients receiving high-dose IL-2, pretreatment factors associated with partial or complete response (P values not adjusted for the number of parameters evaluated) were the absence of a local recurrence ($P = .017$) and greater body weight ($P = .024$). For low-dose IL-2 and subcutaneous IL-2, there were no pretreatment factors associated with response (all $P > .05$). Differences in treatment parameters are not useful in predicting which patients might respond, but rather apply to an understanding of potential mechanisms affecting those responses. Among treatment parameters, an increased probability of response was only associated with a greater number of doses delivered ($P = .035$ for patients on high-dose IL-2, and $P = .022$ for patients on low-dose IL-2; P was not significant for subcutaneous IL-2, but the majority of patients received all 30 allowed doses). A logistic regression analysis was also done for the high-dose arm to see which factors could be associated with response. The factors above remained statistically significant, and corrected calcium also appeared to be important when jointly considered with the other parameters. Pretreatment factors associated with 4-year survival were a lower baseline platelet count (high-dose, $P = .025$; low-dose, $P = .14$; subcutaneous, $P = .049$), and disease confined to lungs (only for low-dose, $P = .019$). For treatment parameters, a response to IL-2 was associated with survival beyond 4 years (high-dose, $P < .001$ for CR; low-dose, $P = .10$ for CR; subcutaneous, $P < .001$ for PR or CR [too few CR alone]). Other factors such as nadir lymphocyte and platelet counts were sporadically associated with better survival for a single treatment arm.

DISCUSSION

The value of IL-2 for patients with renal cancer lies in the small probability that this drug can be curative for some patients with metastatic disease. Variations in the administration of IL-2 that reduce this probability or compromise the completeness or durability of responses will largely obviate the reasons for using this drug. Therefore, it is crucial that regimens that aim to reduce the toxicity of IL-2 do not compromise its activity as measured by response rates and response durations. The importance of this consideration is augmented by recent experiences that demonstrate that the multisystem toxicity encountered with high-dose IL-2 is manageable, and virtually all toxicities short of a treatment-related mortality are completely reversible. As in this report, several groups with experience giving high-dose IL-2 have reported large series of patients with no treatment-related mortality in as many as 809 consecutive patients.[18] Therefore, there is little to justify accepting any reduction in efficacy for the purposes of avoiding toxicity. Furthermore, a quality-of-life assessment on patients in this protocol failed to demonstrate major differences in patient perceptions of toxicity or quality of life between these high- and low-dose regimens.[19] When formally questioned by weekly written evaluation with regards to symptoms, activities of daily living, employment, and global function, patients viewed the more protracted toxicities and inconveniences of subcutaneous therapy as offsetting the more intense but short-lived toxicities of IV therapy. Therefore, antitumor efficacy was identified as the dominant and perhaps only consideration in selecting the optimal method of giving IL-2. The clearest conclusion of this trial was that major tumor regression was significantly more likely if patients received high-dose bolus IL-2, demonstrating that bioactivity of IL-2 is not maximal at the levels attained with either of the low-dose regimens. This is in agreement with preliminary results of a randomized study by McDermott et al[20] where the response rate of high-dose bolus IL-2 was superior to a low-dose subcutaneous regimen that added interferon-alfa as well.

This study failed to show an overall difference in survival for patients receiving high- and low-doses of IL-2 for metastatic renal cancer. This may in part be attributable to the fact that therapies which can benefit or even cure only a minority of patients require extremely large studies to detect overall survival advantages. It is difficult to design a study to demonstrate a difference in long-term cure rate if those rates are below 10%, and some lesser benefit is not evidenced by a significant proportion of the remaining patients. Therefore, response rates and durations of response may better assess therapies such as IL-2. Alternatively, it would be valuable to identify pretreatment characteristics that may select populations more likely to benefit from such therapy and avoid treating most patients without benefit. Our exploratory efforts to analyze patients in this study failed to identify consistent characteristics predictive of a response to IL-2 or to confirm previous efforts in this area. Hypotension requiring vasopressor support and the degree of post-IL-2 lymphocyte rebound, previously described to be associated with higher probabilities of response in patients with melanoma,[21,22] were not found to be similarly associated in patients with renal cell cancer. Previous studies have also reported weak associations between response rates and more doses of IL-2 administered.[22, 23] In this study, the fact that a greater number of doses seemed to be associated with a higher frequency of response was interesting, especially for low-dose IV IL-2, where approximately half of patients stopped for toxicity and half for attaining the maximum allowed number of doses. This would imply that toxicity and efficacy of IL-2 may be separable (with maximal IL-2 delivery being more important than the level of toxicity generated), as patients stopping short of the maximum-allowed number of doses had consistently more side effects (resulting in truncation of therapy), but a lower response rate. Furthermore, there were no associations between maximal levels of toxicity and response rates in any treatment arm. This issue was not as clearly addressed in previous studies with high-dose IL-2 where essentially all patients stop on the basis of reaching maximal toxicity (although patients experiencing milder toxicity typically receive more total doses). This concept requires further validation, and a more

thorough investigation of the molecular nature of the immune response to tumor present in responding patients is needed, which is an area currently being pursued.

In summary, this study supports the finding that low-dose IL-2 regimens can cause the regression of advanced renal cell cancer, but that the higher dose of IL-2 appears to produce greater biologic activity as evidenced by a higher response rate. Still, in the absence of definitive differences in survival, low-dose IL-2 remains a viable therapeutic option for patients with significant medical comorbidities, or for physicians without experience giving high-dose IL-2. When patients and their treating physicians are able to pursue a high-dose IL-2 regimen with a risk of irreversible toxicity or death that is less than 1%, then administering IL-2 at high-doses to patients with metastatic clear-cell renal cancer should be the therapy of choice.

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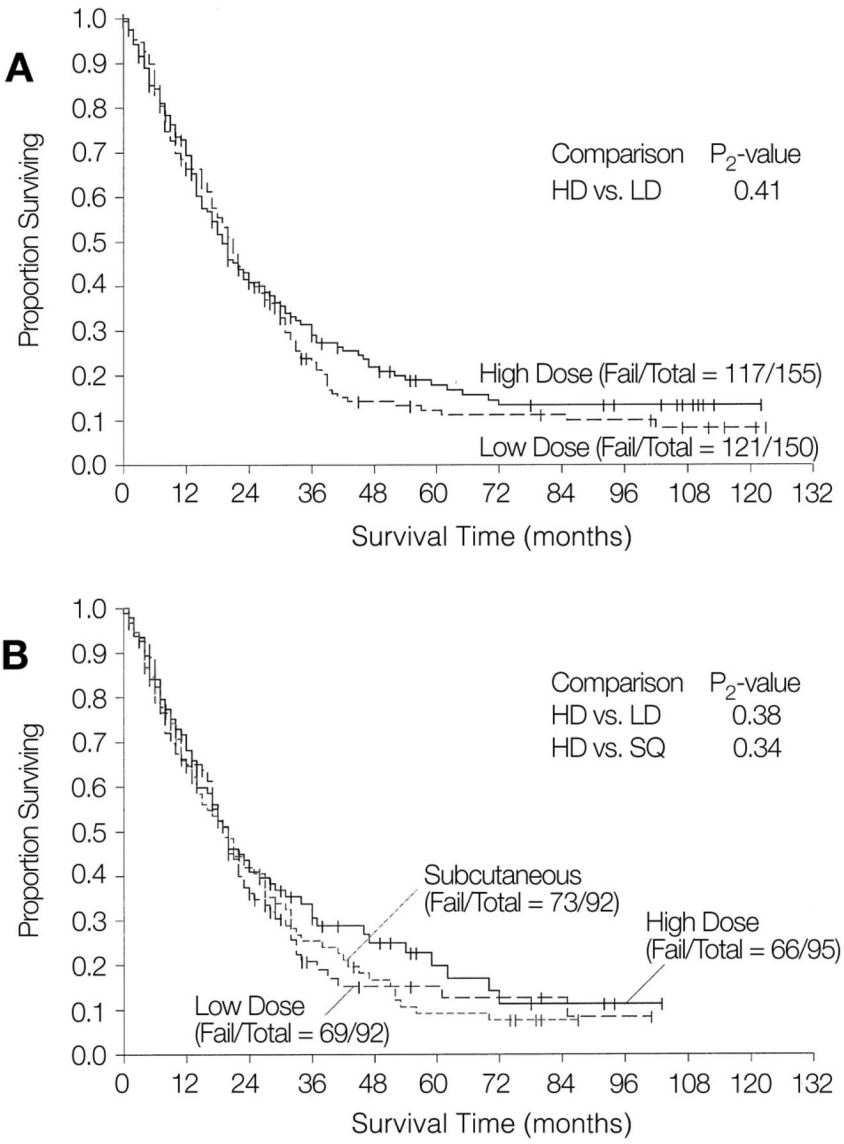

Fig 1.

(A) Overall survival of patients randomly assigned to either low-dose (LD) or high-dose (HD) intravenous (IV) bolus interleukin-2 (IL-2). (B) Overall survival of patients concurrently randomized to received IL-2 by either LD IV bolus, HD IV bolus, or daily subcutaneous (SQ) administration.

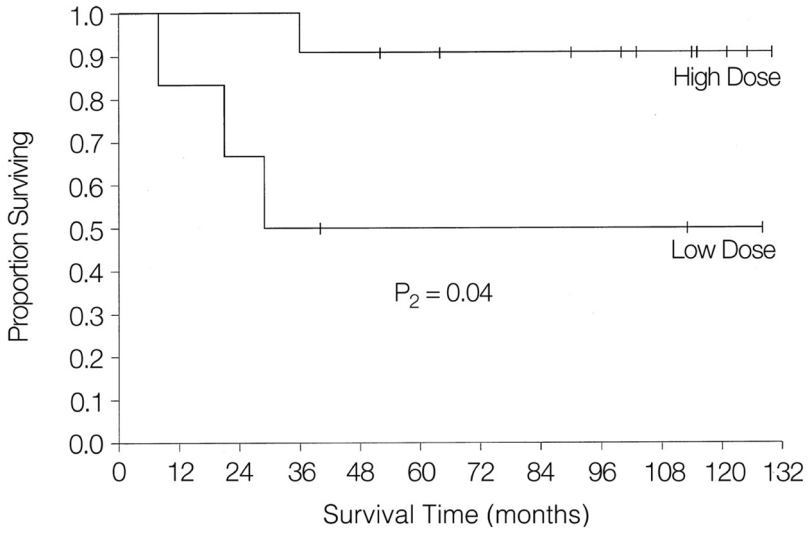

Fig 2.

Survival of patients completely responding to high-dose versus low-dose intravenous interleukin-2.

Table 1

Patient Characteristics and Treatments Administered (all randomly assigned patients)

Variable	No. of Patients		
	High-Dose IV IL-2	Low-Dose IV IL-2	Subcutaneous IL-2
Randomization			
Two-arm randomization	60	57	—
Three-arm randomization	96	93	94
Total	156	150	94
Patient characteristics			
Sex			
Male	110	109	64
Female	46	41	30
Race			
White	135	138	82
Black	9	1	7
Other	12	11	5
ECOG performance status			
0	128	132	78
1	28	17	12
2	0	1	4
Median age, years	48	48	48
Previous therapy			
Surgery	154	147	92
Chemotherapy	9	4	1
Radiotherapy	14	8	9
Immunotherapy	17	12	2
≥ Any two therapies	32	20	11
Treatments administered			
Courses given (n)	285	272	183
Median doses per course	12	27	30
Median total IL-2 per course, million U/kg	8.6	1.9	4.4

Abbreviations: IV, intravenous; IL-2, interleukin-2; ECOG, Eastern Cooperative Oncology Group.

Table 2

Toxicities of All Patients Receiving Interleukin-2 for Renal Cancer: Percentage of Courses With Grade 3 or 4 Toxicity

	High-Dose IL-2	Low-Dose IL-2	Subcutaneous IL-2
Total courses (100%)	285	272	181
Thrombocytopenia	9.2	1.5	0
Hyperbilirubinemia	3.2	0.7	0
ALT	3.2	0.7	0.6
Nausea/vomiting	13.4	8.5	3.3
Diarrhea	9.2	3.7	1.7
Peripheral edema	0.4	2.6	0
Creatinine (≥ 8.0)	1.1	2.6	0.6
Oliguria (≤ 80 mL/8 h)	12.0	7.7	1.1
Pulmonary	4.2	1.1	0
Malaise	20.5	9.9	9.4
Infection	2.8	2.6	1.1
Arrhythmia, atrial	4.2	1.5	0
Hypotension	36.4	2.9	0
CNS level of consciousness	2.5	2.6	0
CNS orientation	10.2	3.7	1.7
Death	0	0	0

Table 3

Response of Patients Randomly Assigned to High-Dose or Low-Dose Intravenous IL-2

	No. of Patients		
	High-Dose IL-2	**Low-Dose IL-2**	**Subcutaneous IL-2**
Two-arm study			
Evaluable patients	155	149	
CR	11	6	
PR	22	13	
Major response rate, %	21	13*	
Three-arm study			
Evaluable patients	96	92	93
CR	6	1	2
PR	14	9	7
Major response rate, %	21	11	10†

Abbreviations: IL-2, interleukin-2; CR, complete response; PR, partial response.

*$P = .048$ by χ^2 test; $P = .067$ by Fisher's exact test *v* high-dose IL-2.

†$P = .033$ by χ^2 test; $P = .043$ by Fisher's exact test *v* high-dose IL-2 (unadjusted).

Table 4

Response Durations

Duration (months)					
High-Dose IV IL-2		Low-Dose IV IL-2		Subcutaneous IL-2	
CR	PR	CR	PR	CR	PR
130+	**37**	128+	**24**	**78**+	**28**
121+	**28**	113+	23	**13**	**28**
115+	**24**	**40**+	22		**17**
114+	**23**	20	**21**+		**15**
103+	**19**	19	**15**		**9**
100+	**17**	3	**13**+		**8**
90+	**17**		11		**2**
52+	16		**11**		
45	15		**8**+		
23	14		7		
19	**14**		**7**		
	14+		**4**		
	13		**4**		
	10				
	9				
	8+				
	8				
	8				
	7				
	6				
	4				
	4				

NOTE. Bold values are for patients concurrently randomly assigned between three arms. + indicates response is ongoing.

Abbreviations: IV, intravenous; IL-2, interleukin-2; CR, complete response; PR, partial response.

Table 5

Potential Prognostic Factors Investigated

	Factors
Pretreatment	Age, sex, race, performance status, weight, height, body mass index, previous treatments, sites of disease (lung, liver, bone, lymph nodes, lung + nodal, local recurrence), time from diagnosis to randomization, baseline laboratory values
Treatment	Doses of IL-2, peak and nadir blood and differential counts, new hypothyroidism, laboratory values, grade 3 to 4 toxicities, response to treatment

Abbreviation: IL-2, interleukin-2.