VOLUME 23 · NUMBER 1 · JANUARY 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Trial of High-Dose Interleukin-2 Versus Subcutaneous Interleukin-2 and Interferon in Patients With Metastatic Renal Cell Carcinoma

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Submitted March 29, 2004; accepted October 6, 2004.

Supported in part by grants to each institution from Chiron Therapeutics, Division of Chiron Corporation, Emeryville, CA; and Schering Plough Corporation, Kenilworth, NJ.

Presented at the 37th Annual Meeting of the American Society of Clinical Oncology, San Francisco, CA, May 12-15, 2001.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/05/2301-133/$20.00

DOI: 10.1200/JCO.2005.03.206

ABSTRACT

Purpose
The Cytokine Working Group conducted a randomized phase III trial to determine the value of outpatient interleukin-2 (IL-2) and interferon alfa-2b (IFN) relative to high-dose (HD) IL-2 in patients with metastatic renal cell carcinoma.

Patients and Methods
Patients were stratified for bone and liver metastases, primary tumor in place, and Eastern Cooperative Oncology Group performance status 0 or 1 and then randomly assigned to receive either IL-2 (5 MIU/m^2 subcutaneously every 8 hours for three doses on day 1, then daily 5 days/wk for 4 weeks) and IFN (5 MIU/m^2 subcutaneously three times per week for 4 weeks) every 6 weeks or HD IL-2 (600,000 U/kg/dose intravenously every 8 hours on days 1 through 5 and 15 to 19 [maximum 28 doses]) every 12 weeks.

Results
One hundred ninety-two patients were enrolled between April 1997 and July 2000. Toxicities were as anticipated for these regimens. The response rate was 23.2% (22 of 95 patients) for HD IL-2 versus 9.9% (nine of 91 patients) for IL-2/IFN ($P = .018$). Ten patients receiving HD IL-2 were progression-free at 3 years versus three patients receiving IL-2 and IFN ($P = .082$). The median response durations were 14 and 7 months ($P = .14$), and median survivals were 17.5 and 13 months ($P = .24$). For patients with bone or liver metastases ($P = .001$) or a primary tumor in place ($P = .040$), survival was superior with HD IL-2.

Conclusion
This randomized phase III trial provides additional evidence that HD IL-2 should remain the preferred therapy for selected patients with metastatic renal cell carcinoma.

J Clin Oncol 23:133-141. © 2005 by American Society of Clinical Oncology

INTRODUCTION

In 1992, the United States Food and Drug Administration approved high-dose (HD) bolus interleukin-2 (IL-2; Proleukin; Chiron, Emeryville, CA) for the treatment of patients with metastatic renal cell carcinoma. Approval was based on the finding that IL-2 induced durable responses associated with prolonged disease-free survival in a small percentage of patients.[1,2] However, this regimen was associated with significant toxicity and cost, and consequently, its application has been limited to highly selected patients treated at specialized centers.[3,4] Several investigators have evaluated regimens containing lower doses of IL-2 in an attempt to decrease toxicity.[5-7] Attempts were also made to improve treatment efficacy by adding interferon alfa-2b (IFN; Intron A; Schering Plough Corporation, Kenilworth, NJ) and then fluorouracil to

low-dose IL-2 regimens. These regimens were reported to produce response rates and survival comparable to those reported for HD IL-2 with much less acute toxicity.[8-12]

In an effort to confirm and extend these results, the Cytokine Working Group (CWG) conducted a series of phase II trials that evaluated HD bolus IL-2 alone, intravenous (IV) IL-2 and IFN, outpatient subcutaneous IL-2 and IFN, and subcutaneous IL-2 and IFN alternating with fluorouracil/IFN in patients with metastatic renal cell carcinoma.[13-15] All patients on these studies had met the same eligibility criteria. The response rates (range, 11% to 17%) and median survivals (range, 15 to 20 months) were similar in these studies, although acute toxicity was less severe in the outpatient regimens. The addition of IV IFN to HD IL-2 and fluorouracil to outpatient IL-2 and IFN did not seem to improve efficacy but did increase toxicity. The median response duration and 3-year progression-free survival seemed to be longest with HD IL-2; however, because these studies were not randomized, patient selection bias could have influenced the results.

This phase II experience encouraged the CWG to formally investigate whether lower-dose IL-2 regimens were able to produce durable responses at a rate similar to HD IL-2 before accepting such regimens as standard therapy.

Therefore, a randomized phase III trial was initiated to compare HD IV bolus IL-2 with outpatient subcutaneous IL-2 and IFN in patients with advanced renal cancer. On the basis of the results of earlier CWG phase II studies, 3-year progression-free survival was chosen as the primary study end point.

PATIENTS AND METHODS

Patient Selection

Eligible patients were required to have histologically confirmed bidimensionally measurable and clearly progressive metastatic renal cancer; an Eastern Cooperative Oncology Group performance status of 0 or 1; adequate organ function, with normal hematologic parameters; serum creatinine $\leq$ 1.5 mg/dL or calculated creatinine clearance greater than 60 mL/min; forced expiratory volume in 1 second greater than 2.0 L/sec or 75% of predicted value; no evidence of congestive heart failure, serious cardiac arrhythmias, symptoms of coronary artery disease, or ischemia on a cardiac stress test; negative serologic testing for human immunodeficiency virus type I antibody and hepatitis B surface antigen; no contraindications to the use of pressor agents; no evidence of active infection requiring antibiotic therapy; and no medical condition requiring corticosteroids. Four weeks were required to elapse since prior therapy; patients who had received prior treatment with either IL-2 or IFN and those with brain metastases, seizure disorders, organ allografts, history of another malignancy, or concurrent corticosteroid therapy were ineligible. The human investigational research committee at each institution approved the protocol at all institutions and voluntary written informed consent was obtained from each patient.

Treatment Plan

Outpatient subcutaneous IL-2 and IFN. On treatment day 1, patients received a subcutaneous IL-2 loading dose of 5×10^6 U/m^2 every 8 hours for three doses. This was followed by a 5×10^6 U/m^2 dose via subcutaneous injection, one dose per day on treatment days 2, 3, 4, and 5 (week 1), and then daily 5 days per week for the remaining 3 weeks as outpatients. During the first 4 weeks of treatment, patients also received subcutaneous IFN 5×10^6 U/m^2/dose thrice weekly. Cycles were repeated every 6 weeks. One cycle consisted of 4 weeks of treatment followed by 2 weeks of rest. Up to 2 weeks of additional rest were allowed for the resolution of adverse events. A maximum of six 6-week cycles were given.

Patients were premedicated with acetaminophen 500 to 650 mg orally every 4 hours (total 2,600 mg to 3,000 mg/d). Oral nonsteroidal anti-inflammatory drugs were administered to patients whose fever was unresponsive to acetaminophen. Opioid analgesia (meperidine 25 to 50 mg orally) was given for severe rigors. Patients were evaluated for tumor response after cycles 1, 2, 4, and 6. Patients with disease progression at any time were ineligible for further treatment. All patients were treated for at least two 6-week cycles unless progressive disease or unacceptable toxicity was encountered. To be eligible for more than two cycles, patients had to have at least stable disease, with some evidence of tumor regression or an objective response, and had to meet baseline eligibility criteria for organ function.

High-dose IV IL-2. Patients received IL-2 600,000 U/kg/dose (Chiron) IV every 8 hours for 5 days (maximum of 14 doses) beginning on day 1 and again on day 15. One cycle consisted of 5 days of treatment, 9 days of rest, 5 more days of treatment, and 9 weeks of rest. A treatment delay of up to 4 weeks was allowed for resolution of side effects between cycles. Patients were eligible to receive a maximum of three cycles of treatment.

Patients underwent placement of a central venous catheter before each course of therapy and received antibiotic prophylaxis with ciprofloxacin 250 mg orally bid on days 1 to 10 and 15 to 24 of each cycle. All antihypertensive therapy was discontinued at least 24 hours before initiating each cycle of IL-2. Patients also received acetaminophen (650 mg orally every 4 hours) and indomethacin (25 mg every 6 hours) to reduce febrile reactions, ranitidine (150 mg) or famotidine (20 mg) orally every 12 hours for prophylaxis of gastrointestinal bleeding, hydroxyzine hydrochloride (25 to 50 mg orally every 6 hours) or diphenhydramine (25 mg orally every hours) for pruritus, meperidine (25 to 50 mg orally every 6 hours) for chills and rigors, an antidiarrheal agent, antiemetics, anxiolytics, diuretics, and vasopressors as needed.

Patients were evaluated for response during week 6 and 12 of the first cycle. To be eligible for more than one cycle of treatment, patients must have had at least stable disease with evidence of some minor tumor regression or objective response and had to meet baseline eligibility criteria for organ function.

Dose Modification and Toxicity Monitoring

Toxicity was evaluated using the National Cancer Institute (NCI) Common Toxicity Criteria version 2.0.

Dose modification for toxicity: IL-2 and IFN. Dose-limiting toxicity (DLT) was defined as grade 3 to 4 toxicity with the exception of cardiac and neurologic toxicity ($\geq$ grade 2) and hematologic and liver toxicity (grade 4). If a patient developed a DLT during weeks 1 to 4 of any cycle, both IL-2 and IFN were held until recovery took place (ie, the DLT improved to grade 1 or less) and then reinstituted with no change in dose. If a DLT recurred, doses for both drugs were reduced by 40% thereafter. If a DLT recurred

at the lower dose, treatment was stopped and the patient was taken off treatment.

Dose modification for toxicity: HD IL-2. Treatment with HD IL-2 was modified by withholding doses of IL-2 rather than continuing therapy at a reduced dose. Doses of IL-2 were withheld for hypotension refractory to fluids and pressors or requiring unacceptably high pressor doses, anuria for more than 24 hours and unresponsive to fluid replacement and low-dose dopamine, respiratory distress requiring more than 4 L of oxygen to maintain O_2 saturation greater than 95%, confusion, sustained ventricular tachycardia or any sign or symptom of myocardial ischemia or myocarditis, metabolic acidosis with HCO_3 less than 18 despite attempts to correct with IV HCO_3; atrial fibrillation, documented systemic infection, or any other serious toxicity that was not controlled at time of next dose.

Response Assessment

Standard response criteria were used. Complete response (CR) was defined as the complete absence of all clinical evidence of malignant disease for at least two determinations 4 weeks apart. Partial response (PR) required a greater than 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions for at least two measurements at least 4 weeks apart. Minor response was defined as less than 50% but more than 25% reduction, but was in fact considered stable disease. Stable disease was defined as including minor response, no change, or less than 25% increase in disease and no new disease. Clinically relevant stable disease had to exceed 6 months. Progressive disease was defined as a greater than 25% increase in the sum of the products of perpendicular diameters of all lesions or the appearance of any new lesion. All patients who achieved a CR or PR had their computed tomography scans audited by independent radiologists to confirm their response and response duration.

Statistical Methods

The primary objective of this phase III study was to determine whether HD IL-2 was superior to outpatient subcutaneous IL-2 and IFN in terms of 3-year progression-free survival. Based on prior studies, it was assumed that the percentage of patients who would remain progression-free at 3 years was 10% for those receiving HD IL-2% and 2% in the IL-2 and IFN arm. The sample size was calculated to detect a difference in 3-year progression-free survival of 8% between the arms with 90% power. We presumed that 5% of enrolled patients would be found to be ineligible. The accrual of 174 patients was required to achieve this power.

After the study was underway, data began to emerge that suggested that patients with non–clear-cell primary tumors did not respond to biologic therapy. The accrual goal was then increased by 10% to permit subset analysis of only clear-cell patients at a later date, thus bringing the final total to 193 patients. Registration and randomization of eligible patients was performed at Beth Israel Deaconess Medical Center. Patients were randomly assigned to one of the two treatment arms in equal proportions using a stratified permuted block randomization. Before randomization, patients were stratified based on Eastern Cooperative Oncology Group performance status (0 or 1), liver or bone metastasis (yes or no), and primary tumor in place (yes or no). Additional prognostic criteria, as described by Motzer et al, [16] were collected from patient records after study completion.

Baseline continuous variables were summarized as median and range and compared between treatment arms using the Wilcoxon rank sum test. Binary baseline and response variables were compared between arms using Fisher's exact test; exact binomial CIs were reported. Three-year progression-free survival and 3-year durable CR were observed for all patients and are analyzed as binary end points. Time-to-event variables were summarized using Kaplan-Meier curves. Response duration was defined from date of documented tumor response to date of documented progressive disease or was censored at date of last follow-up visit; a log-rank test was used to compare treatment arms. Survival end points were defined from date of randomization to date of documented progressive disease (for progression-free survival) or death from any cause or were censored at date of last follow-up visit. Cox proportional hazards regression models were used to estimate hazard ratios and calculate log-rank tests (ie, score test) comparing treatment arms. The model among all patients was stratified by the three randomization strata. For the models by randomization variables, each was stratified for the other two randomization variables. The assumption of proportionality between treatment arms was assessed by plots of log of the cumulative hazard versus time and by testing for an interaction term of treatment arm with time in the model. For patients without liver or bone metastases, the assumption seemed violated, and time-varying hazard ratios were calculated for selected clinically relevant time points. Two-sided *P* values were reported for all analyses. The statistical analysis used SAS 8.2 (SAS Institute Inc, Cary, NC) and StatXact-5 (Cytel Software Corp, Cambridge, MA).

RESULTS

Patient Characteristics

One hundred ninety-three patients were enrolled at 10 participating institutions between April 1997 and July 2000. One patient withdrew consent before treatment and could not be followed-up for any study end point. Ninety-six patients were assigned to each treatment. All patients met the eligibility criteria, but six refused therapy after randomization (five randomly assigned to IL-2 and IFN; one randomly assigned to HD IL-2). These patients were not evaluated for response or progression-free survival but were followed for overall survival. Median duration of follow-up was 4.9 years (range, 3.4 to 6.0 years). The characteristics of patients on this study are listed in Table 1.

Treatment arms were evenly balanced for the stratification criteria and were reasonably well balanced for prior therapy, sex, age, and the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria.[16] Forty-five percent of all patients had liver or bone metastases, 31% had their primary tumors in place, and 87% were intermediate or poor risk by the (MSKCC) prognostic criteria.

Treatment

Treatment information is listed in Table 2. During the first 12 weeks of therapy, patients received most of the planned doses of IL-2 and IFN and 68% of the planned doses of HD IL-2.

Toxicity

The incidence of grade 3 and 4 toxicity in cycle 1 of treatment is listed in Table 3. Grade 3 and 4 toxicities were

Table 1. Patient Characteristics

	% of Patients		
	IL-2 and IFN (n = 96)	HD IL-2 (n = 96)	P*
ECOG PS			.88
0	61	59	
1	39	41	
Liver or bone metastases			.88
No	56	54	
Yes	44	46	
Primary tumor			.88
Out	68	70	
In	32	30	
Sex			.21
Male	64	73	
Female	36	27	
Age, years			.28
Median	56	53	
Range	21-75	25-74	
Prior systemic therapy	3	2	
Motzer prognostic criteria[1]			.25
Good	14	12	
Intermediate	73	82	
Intermediate/poor	3	3	
Poor	10	3	

Abbreviations: IL-2, interleukin-2; IFN, interferon alfa-2b; HD, high-dose; ECOG, Eastern Cooperative Oncology Group.
*Because of inadequate data, six patients could not be classified at all (n = 5, IL-2 and IFN; n = 1, HD IL-2), and six patients may have been intermediate or poor risk.

more common with HD IL-2. In general, the side effects with both treatment regimens were typical of our prior published experience with these regimens.[4,13-15] However, one patient receiving IL-2 and IFN developed acute renal failure while on treatment and required permanent hemodialysis. In addition, two treatment-related deaths were noted, one on each treatment arm. A 44-year-old male patient died during cycle 1, week 4 of IL-2 and IFN of acute respiratory distress syndrome and progressive lung metastases. A 60-year-old male died during cycle 1, week 1 of HD IL-2 as a result of complications from capillary leak syndrome.

Table 2. Planned Treatments Received During Initial 12 Weeks

	IL-2 and IFN, 6-Week Cycles (%)		HD IL-2, 12-Week Cycles (%)	
	Mean	±SE	Mean	±SE
Cycle No. 1				
IL-2	93	16	68	19
IFN	92	18	NA	
Cycle No. 2				
IL-2	95	12		
IFN	95	11		

Abbreviations: IL-2, interleukin-2; IFN, interferon alfa-2b; HD, high-dose; NA, not applicable.

Table 3. Grade 3 and 4 Toxicities in Cycle 1

	IL-2 and IFN (n = 91)		HD IL-2 (n = 95)	
	No. of Patients	%	No. of Patients	%
Constitutional	13	14.3	3	3.2
Hypotension	1	1.1	54	56.8
Gastrointestinal	13	14.3	9	9.5
Hematologic	0	0	13	13.7
Neurologic	3	3.3	14	14.7
Cardiac	0	0	8	8.4
Pulmonary	1	1.1	13	13.7
Renal/electrolytes	3	3.3	13	13.7
Psychiatric	1	1.1	0	0
Hepatic	2	2.2	11	11.6
Infection	0	0	3	3.2

Abbreviations: IL-2, interleukin-2; IFN, interferon alfa-2b; HD, high-dose.

Response Data

Tumor response data by treatment arm are listed in Table 4. The overall response rate to HD IL-2 was 23.2% (95% CI, 15.1% to 32.9%), compared with 9.9% (95% CI, 4.6% to 18.0%) with IL-2 and IFN ($P = .018$). There were eight complete responses (8.4%) with HD IL-2, compared with only three responses (3.3%) on the IL-2 and IFN arm ($P = .214$).

Tumor response data by treatment arm for each of the three stratification criteria are listed in Table 5. Statistically significant differences in response rate favoring the HD IL-2 regimen were seen for patients with liver or bone metastasis ($P = .008$) and primary tumor in place ($P = .024$).

The median response duration for HD IL-2 was 24 months, compared with 15 months for IL-2 and IFN ($P = .180$; Fig 1). The median progression-free survival was 3.1 months for each treatment arm (Fig 2). Ten patients (nine responders and one patient with stable disease) receiving HD IL-2 remained progression-free at 3 years,

Table 4. Summary of Tumor Response Data

	IL-2 and IFN (n = 91)		HD IL-2 (n = 95)		
	No. of Patients	%	No. of Patients	%	P*
Overall response	9	9.9	22	23.2	.018
CR	3	3.3	8	8.4	.214
PR	6	6.6	14	14.7	
Durable 3-year CR	0	0	7	7.4	.014

Abbreviations: IL-2, interleukin-2; IFN, interferon alfa-2b; HD, high-dose; CR, complete response; PR, partial response.
*By Fisher's exact test.

Table 5. Summary of Tumor Response by Randomization Strata

	IL-2 and IFN (n = 91)		HD IL-2 (n = 95)		
	%	No. of Patients	%	No. of Patients	P*
ECOG PS					
0	9.1	5/55	23.2	13/56	.070
1	11.1	4/36	23.1	9/39	.227
Liver or bone metastases					
No	15.4	8/52	23.5	12/51	.329
Yes	2.6	1/39	22.7	10/44	.008
Primary tumor					
Out	14.1	9/64	24.2	16/66	.183
In	0	0/27	20.7	6/29	.024

Abbreviations: IL-2, interleukin-2; IFN, interferon alfa-2b; HD, high-dose; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
*By Fisher's exact test.

compared with three patients (two responders and one patient with stable disease) who received IL-2 and IFN ($P = .082$). Nine of 22 patients who responded to HD IL-2 remain progression-free at 38 to 63 months, whereas only one of nine patients who responded to IL-2 and IFN (a PR) remain progression-free (51 months). There are seven ongoing CRs on HD IL-2 and none on IL-2 and IFN ($P = .014$).

Survival Data

One hundred ninety-two patients were followed up for survival. Survival by treatment arm, stratification subset, and MSKCC prognostic criteria is shown in Table 6. Median survival from time on-study was 13 months for patients assigned to IL-2 and IFN therapy and 17 months for those assigned to HD IL-2. This trend in survival benefit favoring HD IL-2 was not statistically significant ($P = .211$; Fig 3).

A statistically significant survival benefit was noted for patients with liver or bone metastases ($P = .001$) and for patients with primary tumors in place ($P = .040$) with HD IL-2 therapy (Fig 4A through 4F).

Broadly similar results were found when the analysis was limited to the 165 patients with clear-cell histology (77 patients receiving IL-2 and IFN; 88 patients receiving HD IL-2). There was still a significant response difference for patients with liver or bone metastases ($P = .036$), a trend in the number of patients progression-free at 3 years ($P = .067$), and a survival benefit for patients with liver or bone metastases ($P = .002$) or primary tumors in place ($P = .034$) all favoring HD IL-2.

DISCUSSION

Although HD IL-2 produces durable high-quality responses in a small percentage of patients with metastatic renal carcinoma, its toxicity and cost have limited its

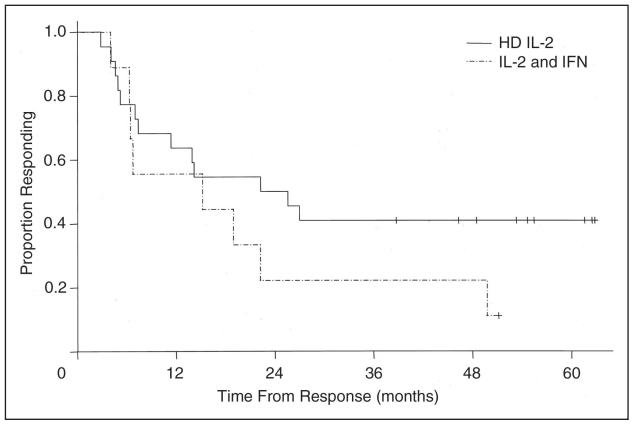

Fig 1. Duration of response to therapy by treatment arm among 31 patients who responded to high-dose interleukin-2 (HD IL-2; n = 22) or IL-2 and interferon alfa-2b (IFN; n = 9). $P = .180$ by log-rank test.

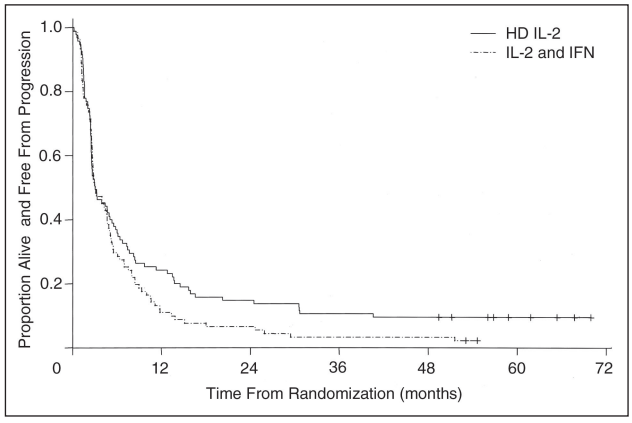

Fig 2. Progression-free survival by treatment arm among 186 patients receiving high-dose interleukin-2 (HD IL-2; n = 95) or receiving IL-2 and interferon alfa-2b (IFN; n = 91). Ten patients receiving HD IL-2 remained progression-free at 3 years compared with three patients who received IL-2 and IFN ($P = .082$ by Fisher's exact test).

Table 6. Summary of Overall Survival, All Patients and by Randomization Strata

	No. of Deaths/Patients	Median Survival (months) IL-2 and IFN (n = 96)	Median Survival (months) HD IL-2 (n = 96)	Hazard Ratio* All Patients	Hazard Ratio* HD	Hazard Ratio* IL-2 and IFN	*P*
All patients	159/192	13.0	17.1	0.81	0.59	1.13	.211
ECOG PS							
0	92/116	19.3	23.5	0.87	0.57	1.32	.509
1	67/76	8.5	9.1	0.74	0.44	1.23	.241
Liver or bone metastases							
No†	86/106	22.1	21.1				—
6 months				2.18	1.08	4.39	
12 months				1.36	0.88	2.12	
24 months				0.91	0.53	1.57	
Yes	73/86	8.0	14.7	0.46	0.28	0.75	.001
Primary tumor							
Out	107/132	18.1	20.7	0.97	0.66	1.43	.878
In	52/60	8.2	12.4	0.54	0.29	0.98	.040
MSKCC criteria							
Good	15/24	26.9	30.9		—		—
Intermediate	121/144	13.9	16.8	0.77	0.52	1.12	.171
Intermediate/poor	5/6	8.2	3.0		—		—
Poor	12/12	3.9	1.6		—		—

Abbreviations: IL-2, interleukin-2; IFN, interferon alfa-2b; HD, high-dose; ECOG, Eastern Cooperative Oncology Group; PS, performance status; MSKCC, Memorial Sloan-Kettering Cancer Center.

*The models for all patients and for MSKCC criteria were stratified for three randomization strata; otherwise models were stratified for the other two randomization strata. *P* values are stratified log-rank tests. Only intermediate MSKCC category was analyzed because of small numbers in other categories.

†For patients without liver or bone metastases, the hazard ratio was not proportional over time and is thus presented as a function of time at three clinically relevant time points. Initially better survival was seen among patients receiving IL-2 + IFN relative to patients receiving HD IL-2, but by 12 months the difference is no longer statistically significant.

application to selected patients treated at specialized centers.[1-4] Lower dose IL-2–based regimens have been reported to produce similar response and survival rates with less toxicity, leading to their widespread use in this patient population.[5-12] Phase II studies conducted by the CWG have suggested that lowering the dose of IL-2 might result in fewer durable responses.[13-15] Before accepting low-dose IL-2 and IFN as standard therapy for metastatic renal cell carcinoma, we designed a randomized phase III study to compare the relative value of HD IL-2 and low-dose IL-2 and IFN.

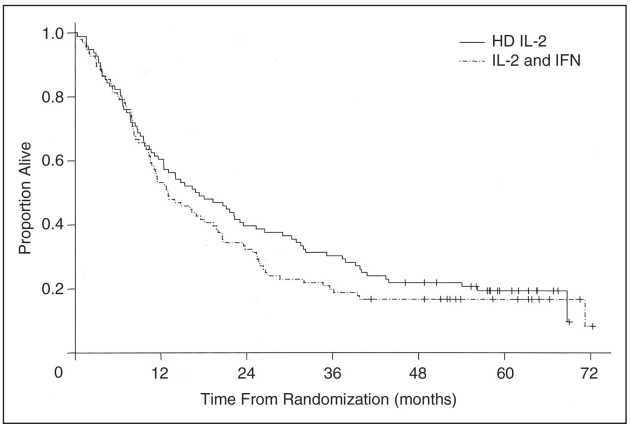

Fig 3. Overall survival among 192 patients randomly assigned to receive high-dose interleukin-2 (HD IL-2; n = 96) or IL-2 and interferon alfa-2b (IFN; n = 96). *P* = .211 by log-rank test.

In this study, HD IL-2 produced a statistically significant improvement in response rate (23.2% *v* 9.9% *P* = .018) compared with IL-2 and IFN. The response quality, as reflected by the CR rate (8% *v* 3%), durable CR rate (7.4% *v* 0%), and response duration (median 24 *v* 15 months) also favored HD IL-2 treatment, although only durable CR rate was statistically significant. HD IL-2 did not have a significant impact on median progression-free survival or median overall survival. Given that IL-2–based therapy for metastatic renal cell carcinoma benefits a minority of patients, we did not expect to see significant differences in these survival end points. However, this study confirmed the observation from prior CWG phase II studies, showing a trend in the number of patients free of disease progression at 3 years (10 *v* three patients; *P* = .082) favoring HD IL-2 therapy.

Patients with performance status ≥ 1, primary tumor in place, or liver or bone metastases have been reported to be less likely to respond to IL-2–based therapy.[17] Consequently, we stratified study patients for these variables. Of note, patients with liver or bone metastases and patients treated with their primary tumor in place had significantly

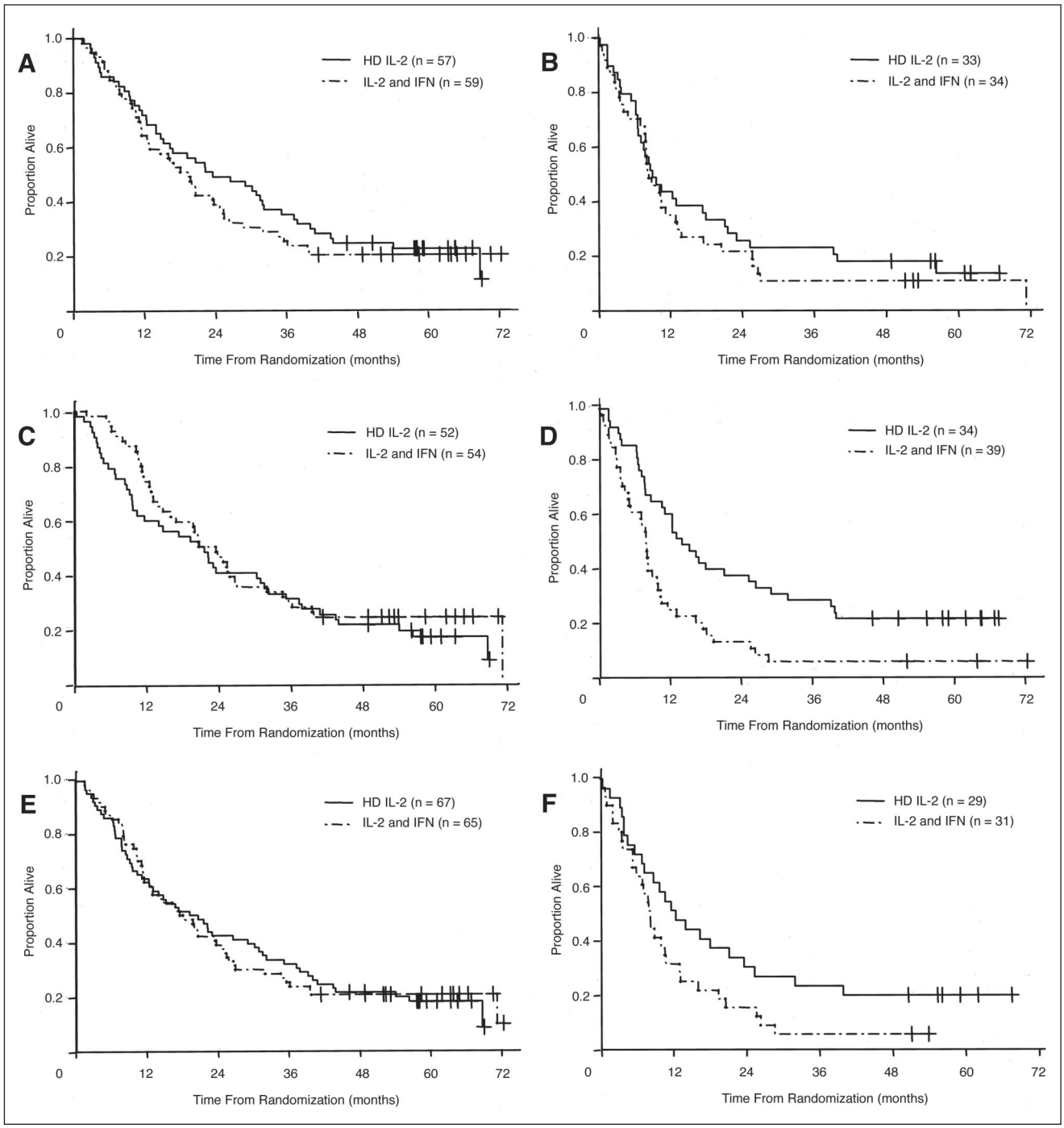

Fig 4. Overall survival among 192 patients randomly assigned to receive high-dose interleukin-2 (HD IL-2) or IL-2 and interferon alfa-2b (IFN). (a) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0; (b) ECOG PS of 1; (c) without liver or bone metastases; (d) with liver or bone metastases; (e) primary out; (f) primary in place.

improved response rates and survival with HD IL-2 relative to lower-dose IL-2 and IFN. The current study represents the first time a survival advantage has ever been shown for any stratified subset of patients receiving IL-2–based therapy. However, the results of the subset analyses should be seen as hypothesis generating and will need to be confirmed in future trials.

Although the response rate for patients receiving HD IL-2 remained relatively constant across all prognostic variables (21% to 24%), IL-2 and IFN was essentially inactive in

patients who had liver or bone metastases or their primary tumor in place. The explanation for this unanticipated result is not readily apparent. It is possible that higher serum or tissue IL-2 levels are needed either to overcome the immune suppression associated with greater tumor burden or to activate T cells in sites of disease other than lung and soft tissue. Consequently, it seems that patients with liver or bone metastases or unresected primaries represent a group of patients who seem to require a more intensive IL-2 regimen to achieve clinical benefit, whereas the impact of dose is less critical in patients with resected primaries and tumor confined to lung.

In contrast to earlier CWG phase II trials, the response rate to HD IL-2 in this study was significantly higher than the response rate with IL-2 and IFN. Considered in the light of this trial, the previously observed similarities in response rates might have been the consequence of less rigorous auditing of the responses in the prior IL-2 and IFN studies than was performed for the HD IL-2 data set that was prepared for United States Food and Drug Administration submission. Although the median response duration seen for patients on the HD IL-2 arm of this study was shorter than in the prior CWG phase II HD IL-2 trial (54 *v* 24 months), the fact that the plateau on the response duration curve falls just below the 50% mark probably accounts for this difference. As expected, HD IL-2 produced more acute toxicity than outpatient IL-2 and IFN. However, holding therapy rapidly reversed most toxicity, and treatment-related mortality occurred in only one patient on each arm.

Other investigators have previously studied the relative value of IL-2–based regimens in patients with metastatic renal cancer. In 1998, the French Immunotherapy Group reported on a large, phase III randomized study that compared inpatient continuous-infusion IL-2 alone with either IFN alone or the combination of IL-2 and IFN.[10] They concluded that the combination of IL-2 and IFN was superior in terms of response rate and 1-year progression-free survival as compared with monotherapy with either agent. This study used an IL-2 regimen that was less intensive than bolus HD IL-2, which may explain the low level of antitumor activity in the IL-2 alone arm (8% response rate). In addition, although IL-2 and IFN produced a superior response rate, this did not translate into more durable responses or an improvement in median or overall survival. In 2003, NCI Surgery Branch investigators reported results of a randomized phase III trial that compared the efficacy and toxicity of HD IV IL-2 to a lower-dose IV regimen (10% of high dose) using an otherwise identical administration schedule.[18] In that study, patients who received HD IL-2 had a significantly higher response rate (21% *v* 13%; $P = .048$) and were more likely to have durable responses than those who received the lower-dose IV regimen. However, there were no significant differences in overall survival between the two groups. Despite the more acute toxicity with the high-dose regimen, quality-of-life assessments showed no differences between the two treatment arms. In an overlapping three-arm study, a third group of patients were randomly assigned to receive a low-dose outpatient subcutaneous IL-2 regimen. In this three-arm comparison, the response rates were 21% for HD IL-2, 11% for lower-dose IV IL-2%, and 10% for subcutaneous IL-2. Once again there were no significant survival differences. In this study, the vast majority of patients had an excellent performance status and had undergone prior nephrectomy, and relatively few had liver or bone metastases, making subset analyses difficult to perform. In the CWG study, most of the trend in survival difference favoring HD IL-2 was attributable to the patient populations with liver or bone metastases and primary tumor in place, perhaps explaining why the survival difference was less pronounced in the NCI Surgery Branch trial. Taking these three randomized studies into consideration, one can conclude that HD IL-2 is superior to both lower doses of IL-2 or IL-2 and IFN in terms of response rates and response quality.

This CWG phase III randomized trial provides additional evidence that HD IL-2 should remain the preferred therapy for selected patients with access to such treatment. Furthermore, it suggests that patients with bone or liver metastases or a primary tumor in place may receive little benefit from a lower-dose IL-2 regimen. Given the toxicity and expense associated with HD IL-2 therapy, and the still-low overall response rate, these results suggest that better criteria for selecting patients for HD IL-2 therapy are necessary. Although some progress has been made in this regard, even with the best selection criteria, the majority of patients will not respond to IL-2 therapy.[19-22] Consequently, new treatment options that focus on important targets (eg, angiogenesis and signal transduction) will still be necessary for those with unfavorable selection features or who experience disease progression after IL-2–based therapy.

Acknowledgment

We thank Judi Manola and Robert Parker for their input on statistical considerations; Susan Graham-McLaughlin and Toneika Allen for assistance in manuscript preparation; and Amanda Youmans, Daniel Clancy, Laura Ruttner, and Christine Connolly for their invaluable assistance with management of the central database.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the past 2 years: Lawrence E. Flaherty, Chiron, Schering; John M. Kirkwood, Schering; Michael S. Gordon,

Chiron; Kim A. Margolin, Chiron, Schering; Michael B. Atkins, Chiron. Performed contract work within the last 2 years: Lawrence E. Flaherty, Chiron, Schering. Received more than $2,000 per year from a company for either of the last 2 years: Joseph I. Clark, Chiron, Schering; Lawrence E. Flaherty, Chiron, Schering; Geoffrey R. Weiss, Chiron, Schering; Jeffrey A. Sosman, Chiron; Marc S. Ernstoff, Chiron, Schering; Kim A. Margolin, Chiron, Schering; Jared A. Gollob, Chiron, Schering; Janice P. Dutcher, Chiron; and Michael B. Atkins, Chiron.

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ERRATA

In the January 1, 2005, Erratum (J Clin Oncol 23:248, 2005), there was an omission.

The erratum was printed without a DOI number. The DOI number for this erratum is 10.1200/JCO.2005.12.910. This omission occurred in the printed issue only, and the DOI is readily available and searchable on www.jco.org.

DOI: 10.1200/JCO.2005.03.905

The December 15, 2004, article by Chi et al entitled, "Feasibility and Response to Induction Chemotherapy Intensified With High-Dose Methotrexate for Young Children With Newly Diagnosed High-Risk Disseminated Medulloblastoma" (J Clin Oncol 22: 4881-4887, 2004) contained an error.

A sentence in the Discussion, in the last paragraph on page 4885, contains a dosage error for craniospinal irradiation. The sentence mistakenly reads, "While craniospinal irradiation is an effective therapy for the treatment of leptomeningeal disease, standard doses of irradiation for leptomeningeal disease (3.6 Gy) result in unacceptable late sequelae in the youngest children." The correct sentence should read, "While craniospinal irradiation is an effective therapy for the treatment of leptomeningeal disease, standard doses of irradiation for leptomeningeal disease (36 Gy) result in unacceptable late sequelae in the youngest children."

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