Phase III Trial of Interferon Alfa-2a With or Without 13-*cis*-Retinoic Acid for Patients With Advanced Renal Cell Carcinoma

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Purpose: **A randomized phase III trial was conducted to determine whether combination therapy with 13-*cis*-retinoic acid (13-CRA) plus interferon alfa-2a (IFNα2a) is superior to IFNα2a alone in patients with advanced renal cell carcinoma (RCC).**

Patients and Methods: **Two hundred eighty-four patients were randomized to treatment with IFNα2a plus 13-CRA or treatment with IFNα2a alone. IFNα2a was given daily subcutaneously, starting at a dose of 3 million units (MU). The dose was escalated every 7 days from 3 to 9 MU (by increments of 3 MU), unless ≥ grade 2 toxicity occurred, in which case dose escalation was stopped. Patients randomized to combination therapy were given oral 13-CRA 1 mg/kg/d plus IFNα2a. Quality of life (QOL) was assessed.**

Results: **Complete or partial responses were achieved by 12% of patients treated with IFNα2a plus 13-CRA and 6% of patients treated with IFNα2a (P = .14). Median duration of response (complete and partial combined) in the group treated with the combination was 33 months (range, 9 to 50 months), versus 22 months (range, 5 to 38 months) for the second group (P = .03). Nineteen percent of patients treated with IFNα2a plus 13-CRA were progression-free at 24 months, compared with 10% of patients treated with IFNα2a alone (P = .05). Median survival time for all patients was 15 months, with no difference in survival between the two treatment arms (P = .26). QOL decreased during the first 8 weeks of treatment, and a partial recovery followed. Lower scores were associated with the combination therapy.**

Conclusion: **Response proportion and survival did not improve significantly with the addition of 13-CRA to IFNα2a therapy in patients with advanced RCC. 13-CRA may lengthen response to IFNα2a therapy in patients with IFNα2a-sensitive tumors. Treatment, particularly the combination therapy, was associated with a decrease in QOL.**

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METASTATIC RENAL CELL carcinoma (RCC) is characterized by a high level of resistance to systemic treatment.[1-3] Cytotoxic chemotherapy and hormonal therapy are ineffective treatments for advanced RCC.[4] Interest in biologic response modifiers has been fostered by a low rate of response to interferon alfa-2a (IFNα2a) and interleukin-2 therapy.[5,6]

13-*cis*-retinoic acid (13-CRA) increased the antiproliferative effects of IFNα2a in several interferon-sensitive renal cancer cell lines.[7] The combination resulted in a 30% response proportion in a phase II trial conducted at our center, which was higher than the proportion earlier achieved with IFNα2a alone.[8] In three other phase II trials, treatment of RCC with IFNα2a plus retinoid was associated with relatively high response rates.[9-11] One treatment program included interleukin-2 with 13-CRA and IFNα2a, and a 22% major response rate was reported.[10] The combination of IFNα2a, 13-CRA, interleukin-2, and fluorouracil was associated with a 44% major response rate.[11] The in vitro and clinical studies provided the rationale for the present randomized trial.

The influence of cytokine treatment on quality of life (QOL) is an important aspect in the management of advanced RCC. The Functional Assessment of Cancer Therapy (FACT) scale[12] was used to assess QOL. Items were appended to the general questionnaire (Functional Assessment of Cancer Therapy-General [FACT-G]) to address the impact of side effects associated with treatment with IFNα2a and the retinoid.

PATIENTS AND METHODS

Patient Selection

Between April 1994 and July 1996, 284 patients were entered onto this randomized trial. Participating centers were Memorial Sloan-Kettering Cancer Center (MSKCC) and member institutions of the

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Eastern Cooperative Oncology Group (ECOG). All patients gave informed consent. Eligibility requirements included the following: histologic confirmation of RCC, bidimensionally measurable disease, Karnofsky performance status (KPS) ≥ 70%, estimated life expectancy more than 3 months, WBC count ≥ 3,000/μL, platelet count ≥ 100,000/μL, serum total bilirubin level less than 1.5 mg/dL (normal, < 1.0 mg/dL), and serum creatinine level less than 2 mg/dL (normal, < 1.1 mg/dL) or creatinine clearance more than 50 mL/min. Patients were excluded if they had received prior systemic chemotherapy or immunotherapy, had received radiation within 4 weeks of study entry, or had brain metastases.

Each patient was evaluated before initiation of treatment. A history was obtained and a physical examination, chest radiography, ECG, automated complete blood cell count, comprehensive blood chemistry panel including determination of cholesterol and triglyceride levels, and appropriate radiographic imaging of measurable disease were performed. A negative pregnancy test result was required for women with childbearing potential.

Treatment Plan

Recombinant human IFNα2a (Roferon-A) and 13-CRA (Accutane) were obtained from Hoffmann-La Roche (Nutley, NJ) through the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD. IFNα2a was provided in 3–million unit (MU) and 18-MU vials and was mixed with sterile water. 13-CRA was available in 10- and 40-mg tablets.

Patients were randomized to daily treatment with IFNα2a plus 13-CRA or IFNα2a alone. IFNα2a was given as a single daily subcutaneous injection, starting at a dose of 3 MU, and the dose was escalated every 7 days by increments of 3 MU, to 9 MU. During escalation, if ≥ grade 2 nonhematologic toxicity or grade 3 hematologic toxicity was noted, dose escalation was stopped. Patients randomized to combination therapy received oral 13-CRA 1 mg/kg/d in two divided doses (rounded to the nearest 10 mg) plus IFNα2a.

Treatment was continued until progression of disease, complete response, or development of toxicity occurred. Dose modifications during therapy were dictated by an attenuation schedule. The IFNα2a dose was attenuated by 3-MU increments in patients with ≥ grade 2 nonhematologic toxicity and grade 3 or 4 leukopenia or thrombocytopenia. In cases of grade 3 or 4 neurologic toxicity (except mood-affecting neurotoxicity), treatment was discontinued and the patient taken off study. In cases of grade 3 or 4 mood-affecting neurotoxicity, the IFNα2a dose was attenuated by 3-MU increments. Patients with fatigue that resulted in a decrease in KPS to ≤ 50% underwent sequential dose reduction and were removed from the study if the participating investigator deemed removal appropriate. If toxicity resulted in an interruption of therapy, patients treated with IFNα2a plus 13-CRA had both drugs withheld. The 13-CRA dose was reduced by 50% in cases of grade 4 dermatologic toxicity or any other grade 3 or 4 toxicity associated with 13-CRA administration.

Patients were monitored weekly for the first 4 weeks of therapy and every 2 weeks thereafter (physical examination, complete blood cell count, and serum chemical analysis). All patients underwent reassessment of measurable disease every 4 weeks until maximum response and every 2 months thereafter. All patients kept daily logs in which they documented symptoms and medications taken.

Standard response and toxicity criteria were used.[13] Stable disease was defined as disease that remained stable for at least 3 months from the day of evaluation after the first cycle of therapy.

Biostatistical Analysis

This trial was designed with response proportion as the major end point. Two hundred eighty-four patients were accrued to detect a 15% difference in response proportion with a power of ≥ 85% and a significance level of 5%. The design included an O'Brien and Fleming stopping rule.[14] As the data accumulated, two interim analyses were undertaken and the data were reviewed by an independent data and safety monitoring committee. Randomization was performed at a centralized office at MSKCC using the method of random permuted block, with center (MSKCC *v* ECOG), lung-only disease, prior nephrectomy, and KPS (70% or 80% *v* 90%) used as stratification factors.[15] All analyses were intent-to-treat analyses. Fisher's exact test was used to compare the response proportions in each treatment arm. Survival curves were estimated using the Kaplan-Meier method[16] and were compared using the log-rank test. The Wilcoxon rank sum test[17] was used to compare the duration of response by treatment arm for patients who achieved a complete or partial response. Durations of best response and survival were measured from the date of initiation of therapy. Toxicity data are summarized as frequency tables, with each patient's worst-grade toxicity over all cycles used in calculations.

QOL Study

Patients enrolled after February 1995 were asked to undergo assessment of QOL. The baseline assessment was performed before therapy, with other assessments performed 2, 8, 17, 34, and 52 weeks after initiation of therapy.

The trial used FACT Version 3 as the tool for QOL assessment.[12] For this trial, 17 disease- and treatment-specific items were developed and appended to the core questionnaire to address symptoms related to treatment with interferon and retinoids. The composite questionnaire was titled the Functional Assessment of Cancer Therapy-Biologic Response Modifier (FACT-BRM). Using an approach combining conceptual input and principal components factor analysis followed by checks on internal consistency, the original pool of 17 statements was reduced to a 16-item measure to assess toxicity related to treatment with biologic response modifiers. The 16-item measure consisted of two subscales to assess toxicity having a physical effect (10 items) and toxicity affecting mood or cognition (six items) (Table 1).

The Trial Outcome Index (TOI), calculated by adding the physical well-being score, functional well-being score, and the two biologic response modifier subscale scores, was used in the following analysis as a summary measure of physical and functional well-being. Time intervals around each scheduled assessment were defined so that each questionnaire received was included in an interval. The compliance rate for each interval was then calculated as the number of questionnaires received divided by the number expected.

A joint mixed-effects and survival model that accounts for unignorable missing data was used to capture changes in QOL over time.[18] Estimates of QOL at baseline and at 2, 8, 17 and 34 weeks were obtained for each arm, and differences between the arms were tested. No estimate of QOL at 52 weeks was obtained for the treatment arms, because there was a paucity of data from that assessment time.

MSKCC Prognostic Model

A prognostic factor model was previously developed using data from 670 patients with advanced RCC treated in 24 MSKCC clinical trials of immunotherapy and chemotherapy between 1975 and 1996.[19] Pretreatment features associated with shorter survival in the multivariate analysis were low KPS (< 80%), high lactate dehydrogenase level (>

Table 1. Two BRM Subscales Formed From Items Appended to the FACT-G Scale*

Physical Toxicity
I get tired easily.
I feel weak all over.
I have a good appetite.
I have pain in my joints.
I am bothered by chills.
I am bothered by fevers.
I am bothered by dry skin.
I am bothered by dry mouth.
I am bothered by dry eyes.
I am bothered by sweating.
Mood-/Cognition-Affecting Toxicity
I have trouble concentrating.
I have trouble remembering things.
I get depressed easily.
I get annoyed easily.
I have emotional ups and downs.
I feel motivated to do things.

*"My thinking is clear" was an additional item in the FACT-BRM, but it was not included in either of the subscales because there was a decrease in the subscales' alpha coefficients when the item was included.

1 5 times upper limit of normal), low hemoglobin level (below lower limit of normal), high corrected serum calcium level (> 10 mg/dL), and absence of nephrectomy. These prognostic factors were used to categorize patients by risk into three groups: those with no risk factors (favorable risk), those with one or two risk factors (intermediate risk), and those with three or more risk factors (poor risk).[19] This risk categorization was applied to the patients on our trial.

RESULTS

Patient Characteristics

Two hundred eighty-four patients were registered onto the trial: 145 received IFNα2a alone and 139 received IFNα2a and 13-CRA. The two treatment arms were similar in terms of patient characteristics (Table 2). Overall median age was 60 years, and 61% of study patients had a KPS of 90%. One hundred seventy-eight patients (63%) had two or more metastatic sites, and 144 (51%) had undergone nephrectomy. Twenty-nine patients (20%) treated with IFNα2a both had undergone nephrectomy and had lung-only metastases, compared with 33 patients (24%) treated with IFNα2a plus 13-CRA. One hundred nine (38%) were registered by MSKCC and 175 (62%) by ECOG.

Response and Survival

Twenty-five (9%) of the 284 patients registered onto the trial had a complete or partial response (Table 3). Complete or partial responses were achieved by 12% of patients treated with IFNα2a plus 13-CRA (five complete responses, 11 partial responses) and 6% of patients treated with IFNα2a (one complete response, eight partial responses; $P = .14$). Five patients (4%) treated with IFNα2a plus 13-CRA achieved a complete response, compared with one (1%) treated with IFNα2a alone ($P = .11$). Median duration of response (complete and partial combined) from the start of treatment in the group treated with the combination was 33 months (range, 9 to 50 months), versus 22 months (range, 5 to 38 months) for the group treated with IFNα2a alone ($P = .03$).

Thirty-seven patients remained progression-free after follow-up: 21 after treatment with IFNα2a plus 13-CRA and 16 after treatment with IFNα2a alone. The median progression-free survival time was 5 months, with no difference in progression-free survival between the two arms ($P = .13$; Fig 1). However, the progression-free survival curves started to separate after 1 year of follow-up. Nineteen percent of patients treated with IFNα2a plus 13-CRA were progression-free at 24 months, compared with 10% of patients treated with IFNα2a alone ($P = .05$).

Fifty-six of 284 patients remained alive, and the median survival time for all patients was 15 months (95% confidence interval, 12 to 17 months). The median follow-up for survivors was 38 months (range, 1 to 62 months); one of these patients was lost to follow-up at 1 month, another at 2 months. There was no difference in survival between the two treatment arms ($P = .26$; Fig 2).

Toxicity

There was no difference in incidence of grade 2, 3, or 4 toxicities between treatment arms (Table 4). Grade 2 toxicities reported in 20% to 40% of patients were leukopenia, anemia, fever, and gastrointestinal toxicity. Grade 3 hematologic toxicities were reported in 60 patients (21%), and grade 4 hematologic toxicities were reported in three patients (1%). A total of 82 grade 3 and 10 grade 4 nonhematologic toxicities were reported in 284 patients.

QOL Analysis

Two hundred thirty patients were asked to participate in the QOL assessment portion of the protocol. A total of 213 patients completed and returned at least one questionnaire; 735 questionnaires were received. The rate of compliance with baseline assessments was 81% in the IFNα2a treatment arm and 86% in the IFNα2a plus 13-CRA treatment arm (Table 5). Over time, compliance rates decreased; by the 52-week assessment, the rates were 24% and 39% in the IFNα2a and IFNα2a plus 13-CRA treatment arms, respectively. There were similar dropout rates in the two arms at each of the assessment times.

The estimates of change in TOI scores are displayed in Fig 3. There was a pattern of decrease in QOL from baseline to 2 weeks and a smaller decrease from 2 to 8 weeks,

Table 2. Patient Characteristics

	IFNα2a (n = 145)		IFNα + 13-CRA (n = 139)		All Patients (n = 284)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	59		61		60	
Range	22-80		27-81		22-81	
Sex						
Male	96	66	93	67	189	67
Female	49	34	46	33	95	33
KPS						
70%	22	15	21	15	43	15
80%	36	25	33	24	69	24
90%	87	60	85	61	172	61
Prior treatment						
Nephrectomy	75	52	69	50	144	51
Radiation therapy	18	12	16	12	34	12
Immunotherapy	0		0		0	
Chemotherapy	0		0		0	
No. of metastatic sites						
Primary or local recurrence only	1	1	1	1	2	1
1	46	32	58	42	104	37
2	46	32	37	27	83	29
3	25	17	24	17	49	17
≥ 4	27	18	19	13	46	16
Sites of metastatic disease						
Adrenal	12	8	10	7	22	8
Bone	37	26	31	22	68	24
Breast	1	< 1	0		1	< 1
Liver	26	18	27	19	53	19
Lung	108	75	88	63	196	69
Lymph nodes	15	10	9	6	24	8
Kidney	10	7	5	4	15	5
Mediastinum	45	31	31	22	76	27
Retroperitoneum	33	23	37	27	70	25
Skin	4	3	4	3	8	3
Soft tissue	22	15	23	17	45	16
Other	15	10	18	13	33	12
Treatment center						
MSKCC	56	39	53	38	109	38
ECOG	89	61	86	62	175	62

especially in the IFNα2a plus 13-CRA treatment arm, making the difference between the arms significant at 8 weeks ($P = .02$). After 8 weeks, there was some recovery of scores in the IFNα2a treatment arm and stabilization of scores in the IFNα2a plus 13-CRA treatment arm, with TOI scores significantly lower at 17 and 34 weeks in the IFNα2a plus 13-CRA treatment arm ($P < .001$ and $P = .01$, respectively). However, scores never recovered to baseline values in either arm.

TOI scores were compared according to risk group as classified by the MSKCC model.[19] Each risk group had a dramatic decrease from baseline to 2 weeks, with the favorable- and intermediate-risk groups having a smaller decrease from 2 to 8 weeks (Fig 4). However, these two groups began to recover after 8 weeks, although a full recovery never occurred. In contrast, the poor-risk group experienced a decrease after 8 weeks, followed by a stabilization of scores at a very low level after 17 weeks. This group never experienced a recovery in scores, and although stabilization did occur after 17 weeks, it was at a level approximately 20 points lower than baseline. The differences between the intermediate- and poor-risk groups at 17 and 34 weeks were significant at the .05 level ($P = .01$ and $P = .03$, respectively).

DISCUSSION

Response proportion and survival did not improve significantly with the addition of 13-CRA to IFNα2a therapy in

Table 3. Response and Patient Status

	IFN-α2a (n = 145)	IFN-α2a + 13-CRA (n = 139)	All Patients (n = 284)
Patients assessable for response	132 (91%)	129 (93%)	261 (92%)
Reasons for inassessable status			
Patient withdrawal	6	2	8
Toxicity	3	5	8
Protocol violation	0	2	2
Other medical conditions	4	1	5
Best response			
Complete	1	5	6
Partial	8	11	19
Minor	11	7	18
Stable disease	69	60	129
Disease progression	43	46	89
Patient status			
Alive with no evidence of disease	1	9	10
Alive with disease	21	23	44
Dead	121	107	228
Lost to follow-up	2	0	2

patients with advanced RCC. The response proportion for patients treated with IFNα2a plus 13-CRA was greater than that for patients treated with IFNα2a, with more complete responses in the combination therapy arm. Moreover, the duration of response for patients who achieved a complete or partial response was longer after treatment with IFNα2a plus 13-CRA than after treatment with IFNα2a alone. However, the overall response proportion for all patients treated on the trial was low (9%), with no significant difference in major response proportion (complete and partial combined) between arms. Two phase III trials are being conducted by others[20,21] and may provide further insight into the role of retinoid-cytokine combination therapy against RCC.

Response proportions in individual phase II trials involving patients with advanced RCC range from 0% to 30% for single-agent IFNα therapy,[5] 0% to 37% for combinations of IFNα2a plus interleukin-2,[22] and 0% to 37% for the three-drug combination of IFNα, interleukin-2, plus fluorouracil.[23] Responsible factors include differences in treatment schedules, sample size, and patient selection. The impact of IFNα2a treatment on survival is controversial, but the two larger phase III trials found IFNα2a therapy to be associated with longer survival than vinblastine or medroxyprogesterone therapy.[24,25] In contrast, no randomized phase III trial has shown a survival benefit for combination therapy compared with treatment with IFNα2a or interleukin-2 alone in patients with advanced RCC.[26-31] Each

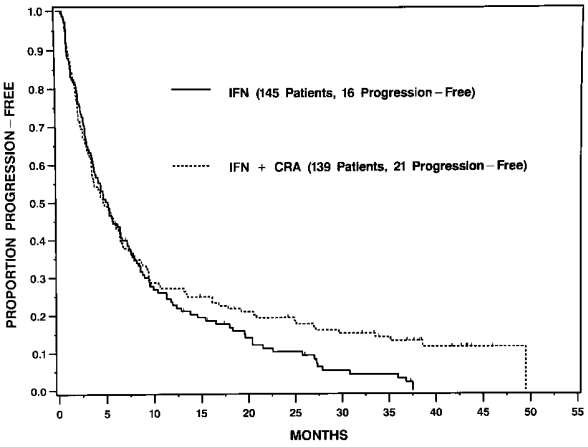

Fig 1. Progression-free survival for patients with advanced RCC treated with IFNα2a versus IFNα2a plus 13-CRA.

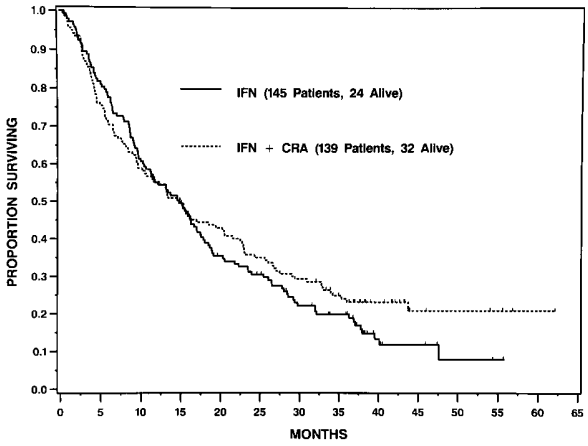

Fig 2. Survival for patients with advanced RCC treated with IFNα2a versus IFNα2a plus 13-CRA. Tick mark indicates last follow-up.

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