A Phase I Study of Subcutaneous Recombinant Interleukin-2 and Interferon Alfa-2a

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Background. **Both recombinant interferon alfa and interleukin-2 (IL-2) have been shown to have some activity as single agents in metastatic renal cell cancer (RCC), although their activity is minimal in more common solid tumors. Recent preclinical studies have suggested that the combination of these two agents is especially promising.**

Methods. **Subcutaneous recombinant interferon alfa-2a and IL-2 were administered at one of five dose levels to 33 patients with refractory solid tumors, including 21 patients with RCC. A constant ratio of 5:1 of interferon alfa-2a to IL-2 was used. Interferon alfa-2a and IL-2 were administered three and five times weekly, respectively, for a total of 4 weeks, followed by a rest of 1–3 weeks between cycles.**

Results. **The dose-limiting toxic effects included hypotension, nephrotoxicity, and fatigue. At the recommended Phase II dose of 7.5 million units (MU)/m² of interferon alfa-2a and 1.5 MU/m² of IL-2, 12 patients were treated. Ten of 12 completed the 4-week cycle without modification. Four patients at that dose level had Grade 3–4 toxic effects. Partial responses were observed in 4 of 16 assessable patients with RCC.**

Conclusions. **Subcutaneous interferon alfa-2a and IL-2 can be self-administered safely on an outpatient basis. At tolerable doses, responses can be achieved in metastatic RCC. *Cancer* 1993; 71:2371–6.**

Key words: interferon alfa, interleukin-2, renal cell carcinoma, Phase I study.

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Supported in part by a Clinical Oncology Career Development Award from the American Cancer Society (to M.J.R.) and a grant from Hoffmann-LaRoche.

The authors acknowledge the important role of Daniel Levitt, M.D., Ph.D., and Jacob Zeffren, M.D., in the initiation and monitoring of this study, and the assistance of Kathy Grefsheim in the preparation of the manuscript.

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Accepted for publication November 4, 1992.

Recombinant interferon alfa has been evaluated in a variety of hematologic malignant conditions and solid tumors. Although highly effective in hairy cell leukemia,[1] it has had limited activity in the more common solid tumors.[2] It has been tested extensively in metastatic renal cell carcinoma (RCC) because of the chemoresistance of this disorder, with an overall response rate of 15–20% at doses resulting in significant toxic effects.[3]

Recombinant interleukin-2 (rIL-2) has been tested less extensively than interferon alfa but appears more promising because of some durable complete responses reported in early studies of this agent.[4] However, there have been substantial toxic effects, often life-threatening, at doses with or without lymphokine-activated killer cells, required to achieve such responses. Although rIL-2 usually is administered intravenously, with a variety of schedules,[5,6] subcutaneous administration is also feasible and results in detectable serum concentrations.[6,7]

The combination of interferon alfa and rIL-2 appears especially promising, based on synergistic activity in preclinical models.[8,9] This study was performed to define a dose and schedule of these two agents that could be administered safely by subcutaneous injection in the outpatient setting. To ensure potentially active doses of both biologics, we used a fixed ratio of interferon alfa and rIL-2, administering both agents at least three times weekly.

Patients and Methods

Patients

Thirty-three patients with metastatic cancer refractory to standard therapy (or for whom standard therapy did not exist) were entered in this trial (Table 1). Other eligibility criteria included a Karnofsky performance status of 70% or greater, hemoglobin level of 10 g/dl or greater, leukocyte count of 3500/μl or greater, platelet

Table 1. Patient Characteristics

Characteristic	No.
Total no. of patients	33
Sex	
Male	27
Female	6
Median age in yr (range)	58 (42–71)
Median Karnofsky performance status (range)	90 (70–100)
Diagnosis	
Renal	21
Colorectal	6
Thyroid	2
Melanoma	2
Gastric	1
Hürthle cell	1
Prior systemic therapy	
None	21
Chemotherapy	11
Immunotherapy	1

count of 100,000/μl or greater, and measurable or assessable disease. Exclusion criteria included significant renal dysfunction (creatinine level > 2.0 mg/dl, nephrotic syndrome), hepatic dysfunction (serum glutamic oxaloacetic transaminase level > 150 IU or four times upper limit of normal, bilirubin level > 1.6 mg/dl, prothrombin or partial thromboplastin time greater than 1.5 times control), pulmonary dysfunction (clinically significant), cardiovascular abnormalities (congestive heart failure, coronary artery disease, cardiac arrhythmias, central nervous system disease (metastases, psychiatric disabilities, seizure disorder), hypercalcemia (total serum calcium level > 12 mg/dl or symptoms), prior rIL-2 and/or interferon alfa, or clinically significant pleural effusions. No patient had major surgery within 3 weeks, chemotherapy or immunotherapy within 4 weeks (6 weeks for mitomycin C, nitrosoureas, or melphalan), or concurrent corticosteroids. All patients provided written informed consent in accordance with institutional and federal guidelines.

Treatment Plan

The first week of treatment was administered in the hospital, and the remainder of therapy was administered on an outpatient basis. Interleukin-2 (rIL-2, Hoffmann-LaRoche, Nutley, NJ) was supplied as 5 million unit (MU) vials and administered Monday through Friday subcutaneously in the morning for 4 consecutive weeks. (The second week of therapy was administered under the direct supervision of a physician.) Interferon alfa-2a (Roferon-A, Hoffmann-LaRoche) was supplied as 18-MU vials and administered subcutaneously Monday, Wednesday, and Friday in the evening for the duration of rIL-2 therapy. Interferon alfa-2a was administered approximately 12 hours after the rIL-2 to facilitate identification of the toxicity of each agent. Cycles were repeated after a rest of 1–3 weeks until progressive disease, dose-limiting toxic effects, or voluntary patient withdrawal.

Cohorts of patients were treated at one of five dose levels, all with a 1:5 ratio of rIL-2 units to interferon alfa-2a units (Table 2). Premedication included 650 mg of acetaminophen orally and 50 mg of diphenhydramine orally. Twenty-five to 50 mg of indomethacin orally every 6 hours was added for refractory toxicity. Twenty-five to 50 mg of meperidine intravenously was administered for severe rigors, except for the last six patients, who were treated as though they were outpatients, although they were staying in the hospital, with no parenteral medications or fluids.

Subsequent Monitoring

Patients were monitored at least weekly as outpatients. Laboratory evaluation included a complete blood count (with differential), serum chemistries, and urinalysis on days 1, 5, 8, 15, and 22 of each cycle. Coagulation studies were obtained biweekly, and an electrocardiogram was obtained on days 1 and 15 of cycle 1 and day 1 of subsequent cycles.

Toxicity Definitions

All toxic effects are reported with the Cancer and Leukemia Group B Expanded Common Toxicity Criteria. However, separate toxicity criteria (Hoffmann-La-Roche) were used to guide treatment decisions during the study. These criteria did not include systemic toxic effects (fatigue, fevers, chills, rigors) and were less conservative in assignment of grade (i.e., Grade 2 azotemia by Roche criteria equivalent to Grade 4 by Cancer and Leukemia Group B Expanded Common Toxicity Criteria). Treatment was stopped for Grade 3 neurotoxicity

Table 2. Dose Levels of Recombinant Interleukin-2 and Interferon

	Dose (MU/m²/d)	
Level	*rIL-2*	*IFN*
I	0.5	2.5
II	1.0	5.0
III	1.5	7.5
IV	2.0	10.0
V	2.5	12.5

rIL-2: recombinant interleukin-2; IFN: interferon; MU: million units.

or cardiotoxicity or any Grade 4 toxic effect and temporarily withheld for other Grade 3 toxic effects.

Response Definitions

For patients with measurable disease, a partial response required a 50% or greater decrease in the sum of the products of the two greatest perpendicular diameters of all measurable lesions for at least 28 days. Progressive disease was defined as a 25% or greater increase in measurable disease or the appearance of new lesions.

Results

Toxic Effects

As shown in Table 3, all 33 patients had chills and/or rigors, with the vast majority also having fever, skin toxic effects, tachycardia, fatigue, elevated hepatic transaminase levels, and nausea/vomiting. Severe fever, fatigue, and transaminase abnormalities occurred in approximately 20% of the patients each. Mild to moderate azotemia occurred in approximately 50% of the patients and was temporally related in many cases to the use of indomethacin.

Grade 3–4 toxic effects were common at all dose levels but dose level I, at which no patient had Grade 3–4 toxic effects (Table 4). The occurrence of Grade 3–4 toxic effects at dose levels II–V was not clearly dose dependent. These were often simply reversible asymptomatic abnormalities in laboratory results, such as neutropenia or hepatic transaminase levels, and did not always result in modification of therapy.

There were only two episodes of Grade 4 toxic effects—thrombocytopenia and transient asymptomatic ventricular tachycardia in one patient each. The thrombocytopenia developed during week 4 of cycle 1 in a man with metastatic colon cancer treated at dose level II. His prior treatment included 5-fluorouracil, carmustine, vincristine, mitomycin C, and methotrexate. The thrombocytopenia was resolved by day 67, but he was not re-treated. The episode of cardiac toxic effects occurred at dose level IV in a woman with metastatic melanoma. She had no prior history of cardiovascular disease but had evidence of cardiomegaly on her baseline chest radiograph. This cardiac event was considered to be possibly related to treatment.

Dose levels IV and V were considered unsuitable for additional outpatient use because of problems with hypotension in 4 of the 12 patients, necessitating modi-

Table 3. Toxic Effects by Grade (Cancer and Leukemia Group B Expanded Common Toxicity Criteria)

	Grade				
Toxic effect	*1*	*2*	*3*	*4*	**Total (%)**
Symptomatic					
Chills/rigors	27	6	0	0	33 (100)
Fever	2	21	7	0	30 (91)
Skin*	21	8	1	0	30 (91)
Tachycardia	18	12	0	0	30 (91)
Fatigue	17	6	6	0	29 (88)
Nausea/vomiting	24	0	1	0	25 (76)
Tachypnea	19	0	0	0	19 (56)
Neurologic	16	1	1	0	18 (55)
Gastrointestinal	16	1	0	0	17 (52)
Hypotension	11	3	2	0	16 (48)
Hypertension	1	1	0	0	2 (6)
Cardiac	0	1	0	1	2 (6)
Laboratory					
Elevated hepatic transaminases	9	11	6	0	26 (79)
Proteinuria	13	5	1	0	19 (58)
Leukopenia	9	6	1	0	16 (48)
Azotemia	9	7	0	0	16 (48)
Neutropenia	6	7	3	0	16 (48)
Anemia	4	3	0	0	7 (21)
Thrombocytopenia	3	0	0	1	4 (12)

* Grade 1, erythema at injection site; Grade 2, diffuse erythema requiring symptomatic treatment; Grade 3, desquamation due to exacerbation of preexisting psoriasis.

Table 4. Incidence of Grade 3–4 Toxic Effects and/or Incomplete First Cycle

Level	No. of patients	Grade 3–4 toxic effects (%)	Incomplete first cycle (%)
I	3	0 (0)	0 (0)
II	6	4 (67)	2 (33)
III	12	4 (33)	2 (17)
IV	6	4 (67)	2 (33)
V	6	5 (83)	4 (67)

fication of therapy (Table 4). Other dose-limiting toxic effects at these two dose levels included proteinuria, neutropenia, fatigue, and nausea/vomiting. Also, six of the seven patients with Grade 3 fever during their first cycle were treated at the two highest dose levels. It was for these reasons that we expanded dose level III, the recommended Phase II dose, from 6 to 12 patients. A detailed analysis of toxic effects at this dose level is shown in Table 5.

Responses

Responses were observed in 4 of 16 patients with measurable metastatic RCC. All four who responded had pulmonary metastases. In addition, one patient who responded had hepatic metastases. None of those who responded had prior therapy, although one patient who responded had received megestrol acetate because of anorexia and weight loss. Two patients who responded were treated at dose level II and two at dose level V. All four responses were partial, ranging from a 70% to 96% decrease (median, 80%) in tumor area. No responses were observed in tumors other than RCC.

Discussion

Our study is consistent with the recent report of Atzpodien et al.,[10] demonstrating that rIL-2 and interferon alfa can be administered safely at effective doses by subcutaneous injection. That study used rIL-2 (Euro Cetus, Amsterdam, Netherlands) and interferon alfa-2b (Essex-Schering, Munchen, Germany) on a different schedule: 9 MU/m^2 of rIL-2 subcutaneously every 12 hours for 2 days, then 1.8 MU/m^2 five times weekly for 6 weeks, with 5 MU/m^2 of interferon alfa-2b three times weekly for the duration of rIL-2. With World Health Organization toxicity criteria, most patients experienced only Grade 1–2 toxic effects, and five responses (including one complete response) were observed among 14 assessable patients with RCC. An update of that data on 34 assessable patients now includes 10 patients who responded, with 4 responding completely.[11] No other doses were evaluated. Other investigators also have developed regimens for outpatient ad-

Table 5. Toxic Effects by Grade at Recommended Phase II Doses (Recombinant Interleukin-2, 1.5 MU/m^2; Interferon, 7.5 MU/m^2)

	Grade				
Toxicity	*1*	*2*	*3*	*4*	Total (%)
Symptomatic					
Chills/rigors	11	1	0	0	12 (100)
Fevers	7	5	0	0	12 (100)
Skin	8	3	0	0	11 (92)
Fatigue	5	3	3	0	11 (92)
Nausea/vomiting	11	0	0	0	11 (92)
Tachycardia	6	3	0	0	9 (75)
Gastrointestinal	7	1	0	0	8 (67)
Tachypnea	7	0	0	0	7 (58)
Neurologic	5	0	0	0	5 (42)
Hypotension	1	0	0	0	1 (8)
Cardiac	0	0	0	1	1 (8)
Laboratory					
Elevated hepatic transaminases	8	3	1	0	12 (100)
Proteinuria	6	2	0	0	8 (67)
Leukopenia	4	2	1	0	7 (58)
Azotemia	6	1	0	0	7 (58)
Neutropenia	1	3	1	0	5 (42)
Anemia	2	2	0	0	4 (33)

MU: million units.

Table 6. Phase I–II Trials of Recombinant Interleukin-2/Interferon Alfa in Renal Cell Carcinoma

Reference	No. of patients	No. of responders (%)	Dose/schedule		Duration of initial cycle (wk)
			rIL-2	*Interferon alfa*	
11	34	10 (30)	3.6–4.8 MU/m² sc qd × 5	3–6 MU/m² sc tiw	6
12	15	6 (40)	1–2 MU/m² cvi qd × 5	3–12 MU/m² im tiw	4
13	5	0 (0)	1–3 MU/m² cvi qd × 4	2–10 MU/m² im qd × 4	4
18	12	1 (8)	0.1–2 MU/m² iv tiw	0–10 MU/m² im tiw	4
19	35	11 (31)	1–4.5 MU/m² iv tid × 5 d	3–6 MU/m² iv tid × 5 d	2
20	41	5 (12)	18 MU/m² cvi qd × 5	3 MU/m² sc qod	2
21	24	3 (12)	4.5 MU/m² iv tid × 5 d	3 MU/m² iv tid × 5 d	2
22	2	1 (50)	1–4 MU/m² iv (2 h) qd × 5	6 MU/m² im tiw	4
23	22	8 (37)	"High-dose"	"High-dose"	Not stated
24	12	4 (33)	18 MU/m² cvi d 1–5, 12–16 (plus LAK)	5 MU/m² im d 12–16	5
25	30	9 (30)	2 MU/m² cvi qd × 4	6 MU/m² im d 1, 4	4
26	19	3 (19)	18 MU/m² cvi d 8–12	10 MU/m² sc d 1–5	2
27	24	1 (4)	3 MU/m² cvi qd × 4	6 MU/m² sc d 1, 4	2
28	15	4 (26)	3 MU/m² cvi qd × 4	5 MU/m² im. qd × 4	4
29	34	4 (12)	3 MU/m² cvi qd × 4	5 MU/m² sc qd × 4	3
30	29	5 (17)	2 MU/m² cvi qd × 5	9 MU/m² sc tiw	4
31	28	3 (11)	0.6 MU/kg iv tid × 5 d	3 MU/m² iv tid × 5 d	2
Current study	16	4 (25)	0.5–2.5 MU/m² sc qd × 5	2.5–12.5 MU/cm² sc tiw	3
Total	397	82 (21)			

rIL-2: recombinant interleukin-2; sc: subcutaneously; qd: daily; tiw: three times weekly; im: intramuscularly; cvi: continuous intravenous infusion; iv: intravenously; tid: every 8 hours; qod: every other day; LAK: lymphokine-activated killer cells; MU: million units.

ministration of rIL-2 in combination with interferon alfa,[12,13] administering rIL-2 by continuous intravenous infusion. Antitumor activity was mentioned in RCC[12] and melanoma.[13]

The single-agent activity of interleukin-2 (IL-2) with or without lymphokine-activated killer cells ranges from 0%[14,15] to 35%.[4,16] A recent extensive summary of the single-agent activity of IL-2 by Parkinson et al. estimated a response rate of 9–16%.[17]

The single-agent activity of interferon alfa is within the same range.[3] In Table 6, we summarize the results of 17 other Phase I or II trials of IL-2 in combination with interferon alfa in various doses and schedules. Many have been reported only in abstract form to date. The overall collective response rate of 21% suggests that additional incremental improvements in therapy of metastatic RCC are sorely needed.

This particular dose and schedule of rIL-2/interferon alfa may be an ideal basis for the additional development of combination cytokine therapy. Although we recommend rIL-2 at 1.5 MU/m² for 5 days weekly and interferon alfa-2a at 7.5 MU/m² for 3 days weekly, this was based on the empiric selection of a 1:5 dose ratio, and other doses and schedules may be equivalent or superior. The toxic effects appear to be cumulative, and we would recommend a treatment duration of 3 weeks with a 2-week rest for broad Phase II testing. The ability to administer rIL-2 (with interferon alfa-2a) to a large number of patients without admission to the hospital will facilitate wider evaluation of this combination immunotherapy approach. As an example, a Phase II study of this regimen in refractory breast cancer has been initiated in the Cancer and Leukemia Group B. Additional testing in RCC and melanoma and/or comparison with more intensive rIL-2–plus lymphokine-activated killer cell regimens also may be indicated.

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