Clinical Studies of Recombinant Interferon Alfa-2a (Roferon®-A) in Cancer Patients

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A Phase I study of interferon alfa-2a was conducted in 20 patients with disseminated cancer to establish the relationship between dose and interferon-related side effects. Fever was the most common side effect, and was not dose-related. Other side effects not related to dose included flu-like symptoms, gastrointestinal symptoms, and numbness of fingers and toes. A dose-response relationship was seen for leukopenia, thrombocytopenia, and the elevation of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). A Phase II study was then conducted in 641 patients to evaluate the efficacy of interferon alfa-2a in a number of disseminated malignant neoplasms. The 415 male and 226 female patients, almost all of whom had malignancies refractory to standard therapy, were treated with interferon alfa-2a at an initial daily dose of 3×10^6 U for 3 days. Doses were increased gradually at 3- to 7-day intervals until the therapeutic dosage was established. The daily dose could not exceed 50×10^6 U, and treatment was continued for at least one month. Efficacy rates, for 65 patients who achieved partial or complete responses, based on the total number of evaluable patients by cancer type were: 11/49 (22.4%), multiple myeloma; 4/21 (19%), lymphomas; 15/108 (13.8%), renal cell carcinoma; 2/30 (6.6%), bladder cancer; 4/39 (10.2%), brain tumors; 5/26 (19.2%), melanoma; 12/12 (100%), cutaneous lymphoma; 10/19 (52.6%), other skin cancers; 2/30 (6.6%), bone and soft tissue sarcomas. Overall, 65/371 (17.5%) of evaluable subjects responded.

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A PHASE I TRIAL was conducted to determine the pharmacokinetics of interferon alfa-2a (Roferon®-A, Hoffmann-La Roche Inc., Nutley, NJ) administered in different doses and to determine the relationship between dosage and the nature and incidence of adverse reactions and laboratory abnormalities. A Phase II trial of interferon alfa-2a was then conducted in 641 cancer patients refractory to conventional therapy.

Phase I Study in Cancer Patients

This trial was conducted with interferon alfa-2a at nine Japanese medical centers between March and May 1982.

Materials and Methods

Twenty patients with disseminated cancer originating at various primary sites were entered. Interferon alfa-2a was administered as a single intramuscular injection of either 18×10^6 U (3 patients), 36×10^6 U (4 patients), 50×10^6 U (6 patients), 75×10^6 U (3 patients), or 100×10^6 U (4 patients). Patients were then observed for 72 hours, and blood was obtained at various times for laboratory study and determination of serum interferon levels.

Results

Adverse reactions: Adverse reactions associated with the single intramuscular injection of interferon included fever, flu-like symptoms, gastrointestinal (GI) symptoms, and numbness of fingers and toes.

Fever, to a maximum temperature of 39°C to 40°C, was observed initially in all patients between 1 and 8 hours after injection, but usually disappeared in 24 to 72 hours. A higher body temperature was associated with a dose of 50×10^6 U or greater (Fig. 1).

Flu-like symptoms included headache, chills, fatigue, and low back pain. Chills occurred in nine patients (45%), fatigue in seven (35%), headache in four (20%), and low back pain in one. Flu-like symptoms essentially disappeared 24 to 72 hours after injection.

Gastrointestinal symptoms, including anorexia and nausea or vomiting, occurred in eight patients (40%). Three patients reported anorexia, and nausea or vomiting was reported by five. GI symptoms resolved in 24 to 48 hours after injections.

Two patients who received a dose of 100×10^6 U reported numbness of fingers or toes of minimal severity, which resolved in 24 to 48 hours.

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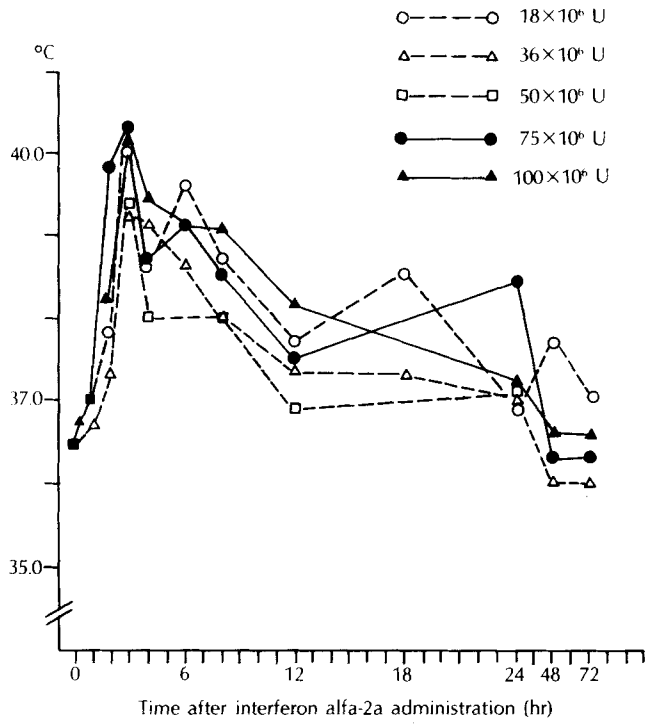

FIG. 1. Body temperature in response to dose in Phase I study of interferon alfa-2a.

Laboratory tests: Laboratory tests showed leukopenia (granulocytes and lymphocytes), thrombocytopenia, and elevated levels of serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), and creatinine.

Dose (×10⁶ U)	18	36	50	75	100
No. of patients	3	4	6	3	4
Adverse reactions	Number and grade*				
Fever	◒ ◒ ◒	◒ ◒ ◒ ◒	● ○ ◒ ◒ ◒ ◒	◒ ● ●	◒ ◒ ● ◒
Headache	○	◒	◒		○
Chills	○	● ◒	● ◒ ◒ ●	●	◒
Fatigue	◒	◒ ○		◒ ○	○ ○
Anorexia	○	◒			○
Nausea, vomiting		○ ● ◒	◒		◒
Lumbago					○
Numbness					○ ○
Leukopenia	○ ○	○ ○ ○	○ ◒ ○ ○	○ ○ ◒	◒ ◒
Granulocytopenia		○		○	◒ ○
Thrombocytopenia		○	○ ○◒		○ ◒
SGOT ↑			○	○ ○ ◒	○
SGPT ↑				○ ◒	○
LDH ↑				◒	
Creatinine ↑			○		

* Grade: ○ minimal, ◒ moderate, ● severe

FIG. 2. Adverse reactions and frequency by dose of interferon alfa-2a in Phase I study.

Leukopenia was seen in 14 patients (70%); it was minimal in ten of these and moderate in four. The leukocyte count (WBC) returned to normal within 2 to 4 weeks, but returned to normal more promptly in the four patients with granulocytopenia only. Thrombocytopenia was seen in six patients (30%) and returned to normal within 7 days. SGOT elevation occurred in five patients, SGPT elevation in three patients, and LDH and creatinine elevation in one subject each; all returned to baseline in 7 days. A dose-response relationship was seen for leukopenia, thrombocytopenia, and elevation of SGOT and SGPT (see Fig. 2).

Pharmacokinetics: Pharmacokinetic data were derived from serum interferon concentrations by bioassay in 18 evaluable patients. Serum concentrations increased with higher doses (Fig. 3). Time to maximum concentration (T_{max}) varied from about 4 to 8 hours, and elimination half-life ranged from 5.4 to 28.7 hours, regardless of the dose. Area under the curve (AUC) also increased with increasing doses (except at 18×10^6 U due to laboratory error). Data are summarized in Table 1.

Other studies: Antibodies to interferon alfa-2a were sought before and one week after injection, but were not detected in any patient. All patients were examined by prick test before injection and all tests were negative.

These results indicated that higher doses of interferon alfa-2a tend to be associated with a higher incidence of adverse reactions and laboratory abnormalities, although this agent was well tolerated by all patients.

Phase II Study in Cancer Patients

A Phase II trial of interferon alfa-2a was conducted in a collaborative study at 134 Japanese medical centers.

Materials and Methods

Patients considered for entry into the study had confirmed disseminated malignant neoplasms, refractory to standard therapy.

They were treated with interferon alfa-2a at an initial daily dose of 3×10^6 U for 3 days, given intramuscularly, with dosage gradually increased (3 to 6 to 9 to 18 to 36 to 50×10^6 U/day at intervals of 3 to 7 days) to a dose they were able to tolerate for the duration of therapy, which was at least one month. The total daily dose was limited to a maximum of 50×10^6 U.

The effects of therapy were evaluated by physical examination, vital signs, neurological examination, electrocardiogram, chest x-ray, examination of intramuscular injection site, blood chemistry analysis, urinalysis, immune studies, prick test, serum interferon concentrations, antibodies to interferon alfa-2a, and other laboratory tests.

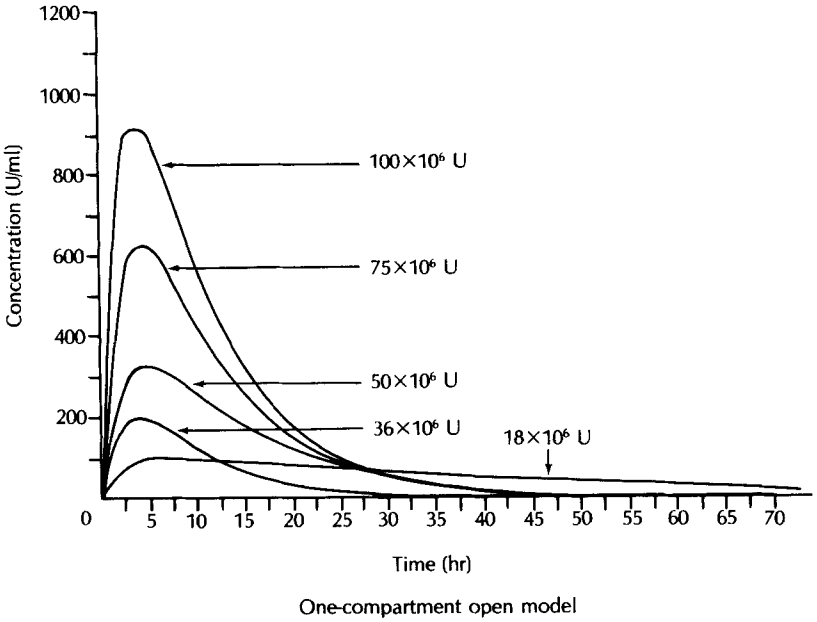

FIG. 3. Serum interferon concentrations (U/ml) in response to dose in Phase I study.

Results

Of the 641 patients entered in the study (415 males and 226 females) 371 were considered to be evaluable. The remaining 270 patients were excluded, 150 because of insufficient washout period, 22 because they received concomitant therapy, 88 for insufficient dose levels, and 10 because of inadequate evaluation.

Of the 371 evaluable patients, 15 achieved a complete response, 50 a partial response, 28 a minor response, 182 showed no change, and disease progressed in 96.

Grouped by type of cancer (Table 2), complete (15) and partial (50) responses were seen in: 11 of 49 (22.4%) evaluable patients with multiple myelomas, 4 of 21 (19%) evaluable patients with various lymphomas, 15 of 108 (13.9%) evaluable patients with renal cell carcinoma, 2 of 30 (6.7%) evaluable patients with bladder cancer, 4 of 39 (10.3%) evaluable patients with brain tumor, 5 of 26 (19.2%) evaluable patients with melanoma, 12 of 12 (100%) evaluable patients with cutaneous lymphoma, 10 of 19 (52.6%) evaluable patients with other skin cancers, and 2 of 30 (6.7%) evaluable patients with bone and soft tissue sarcomas. Overall, 65 of 371 (17.5%) evaluable patients responded to therapy.

In treating malignant skin cancers, it was found that local injection was more effective than intramuscular injection for inducing tumor regression.

The duration of therapy and total dose at which there was at least a 50% regression of tumor are presented in Table 3. The mean duration of response was 77 days with multiple myeloma, 110 days with renal cell carcinoma,

TABLE 1. Pharmacokinetic Parameters of Interferon Alfa-2a Serum Concentrations

Dose ($\times 10^6$ U)	No.	T max (hr)	C max (U/mL)	t 1/2 (hr)	AUC (U·h/ml)
18	4	7.64	101	28.70	5050
36	3	3.88	200	5.41	2560
50	4	5.01	325	8.59	6040
75	4	4.27	615	6.49	9080
100	3	3.96	921	5.76	12300

T max: time to maximum concentration; C max: maximum concentration; t 1/2: elimination half-life; AUC: area under the curve.

TABLE 2. Clinical Effects in Phase II Study of Interferon Alfa-2a in Cancer Patients

	No. of patients entered	Response					No. of evaluable patients
		CR	PR	MR	NC	PD	
Multiple myeloma	66	1	10	5	32	1	49
Lymphoma, *etc.*	55		4	2	13	2	21
Renal cell carcinoma	208	2	13	10	51	32	108
Bladder cancer, *etc.*	61		2		16	12	30
Brain tumor	82		4	2	23	10	39
Melanoma	31		5	3	12	6	26
Cutaneous lymphoma	16	9	3				12
Other skin cancers	23	3	7	3	5	1	19
Stomach cancer	14			1	4	3	8
Colon cancer	7				4	1	5
Lung cancer	18			1	5	3	9
Breast cancer	22				6	9	15
Bone and soft tissue cancer	38		2	1	11	16	30
Total	641	15	50	28	182	96	371

CR: Complete response; PR: partial response; MR: minor response; NC: no change; PD: progressive disease.

TABLE 3. Clinical Effects of Interferon Alfa-2a in Cancer Patients*

	No. of patients	Treatment period (days)	Total dose ($\times 10^6$ U)
Multiple myeloma	11	40	511
Renal cell carcinoma	15	61	696
Brain tumor	4	55	534
Malignant skin tumors (cutaneous malignant lymphoma)	26	30	87

* Average treatment period and average total dose to 50% regression or more.

84 days with brain tumor, and 70 days with malignant skin cancer.

Adverse reactions and/or toxicity occurred in 571 of the 641 patients entered (89.1%), as seen in Table 4. Fever developed in 1 to 7 days after the initiation of treatment, and disappeared in most cases within 2 weeks. Patients seemed better able to tolerate fever over time. Anorexia generally developed within 2 weeks of the initiation of therapy, and generally disappeared by 4 weeks. Nausea and vomiting developed by the first to the 14th day of treatment, and generally resolved within 4 weeks. Patients reporting fatigue noted its occurrence from 1 to 14 days after treatment began; fatigue resolved or improved within 4 weeks in approximately 60% of the reporting patients.

Leukopenia and thrombocytopenia were usually seen within 2 to 4 weeks of treatment, and disappeared or improved by the fourth week. SGOT and SGPT levels most commonly increased between 15 and 30 days of treatment,

TABLE 4. Main Side Effects* in Phase II Study of Interferon Alfa-2a in 641 Cancer Patients

	No. of patients with side effects	% of total
Fever	387	60%
Anorexia	194	30%
Nausea, vomiting	108	17%
Fatigue	137	21%
Leukopenia	273	43%
Thrombocytopenia	151	25%
Elevation of SGOT level	186	30%
Elevation of SGPT level	166	27%

* Other side effects: chills, headache, diarrhea, stomatitis, myalgia, alopecia, apathy, skin eruption, anemia, hemorrhagic tendency, oligochromemia, oligocythemia, elevations of lactic dehydrogenase and alkaline phosphatase.

SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

TABLE 5. Antibodies to Interferon Alfa-2a in Phase II Study

No. of patients examined	292
No. of patients detected	37
Detection rate	12.7% (37/292)
Average detection period (days)	80
Average cumulative doses to detection period	1121×10^6 U

and in most instances therapy was not discontinued. Return to normal or improvement occurred within 6 weeks in most cases.

Antibodies to interferon alfa-2a were sought in 292 patients. Elevated antibody titers were observed in 37 of these patients (12.7%). The mean duration until detection was 80 days, and mean cumulative dosage until detection was 1121×10^6 units (Table 5). Of the 37 patients with elevated antibody titer, two achieved a complete response and three a partial response. Two of the three partial responders achieved a reduction in tumor size of 50% or more for more than one month consecutively *after* elevation of antibody titer. There was no specific side effect that could be attributed to elevated antibody titer. Anti-*Escherichia coli* antibodies and anti-mouse immunoglobulin G antibodies, which might have been mixed in the manufacturing process of interferon alfa-2a, were detected in 59 patients, none of whom developed antibodies to interferon alfa-2a.

Discussion

Side effects attributable to interferon alfa-2a in this study are primarily constitutional, minimal to moderate in severity, and self-limited, usually resolving in 2 to 4 weeks with continued administration. Fever and leukopenia are the two drug-related adverse reactions most often observed (60% and 43%, respectively). Fever does not appear to be dose-related, but leukopenia does. Patients generally tolerate interferon-related side effects well. Thus, toxicity should not deter a trial of interferon in patients with neoplasms refractory to standard therapeutic modalities. The principal determinant of interferon use is efficacy.

Sixty of 371 evaluable patients (16.2%) unresponsive to previous treatment achieved a complete or partial response with interferon. Nine of 12 evaluable patients with cutaneous lymphoma achieved a complete response and the remaining three achieved a partial response to interferon. These limited data suggest that cutaneous lymphoma may be particularly responsive to interferon.