Treatment of Multiple Myeloma With Recombinant Interferon Alfa-2a

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A Phase II study of interferon alfa-2a was conducted in 64 patients with multiple myeloma (42 IgG, 16 IgA, 5 Bence-Jones type, and 1 IgD) in a multi-institutional cooperative trial. Partial remission was obtained in 10 (21.3%) of 47 evaluable patients, and minor responses in 5 (10.6%) of 47. Remission was reached at 22 to 89 days (median, 29 days) after the initiation of interferon alfa-2a and lasted 4 to 55 weeks (median, 8 weeks). Side effects were noted in more than two-thirds of patients, and included fever (58%), malaise (20%), anorexia (52%), nausea-vomiting (26%), lethargy (2%), and myelosuppression (56%). They were all reversible on discontinuation of interferon alfa-2a. Antibody to interferon alfa-2a was detected in 1 of 20 patients tested during the course of treatment. Thus, interferon alfa-2a was effective in multiple myeloma, producing unequivocal response in 21.3% of patients without unacceptable side effects.

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IN ADDITION TO ANTIVIRAL ACTIVITY, interferons are known to possess antitumor activities against spontaneous and transplantable animal tumors of both viral and nonviral origin.[1] Recently, human interferons have been shown to possess antitumor properties against various human malignancies, including osteogenic sarcoma, malignant lymphoma, multiple myeloma, leukemia, and renal cell carcinoma.[2–8] Although the true biological function of interferons in human malignancy remains largely speculative, they seem to possess both a direct cytotoxic effect on tumor cells and an indirect effect mediated through immune systems.[1] Because of the species-specific activities of interferons, the early clinical trials were restricted by the limited supply and high costs. The recent progress of recombinant DNA technology, however, has provided a method of producing large quantities of highly purified single molecular interferons.

We report here the results of a Phase II multi-institutional cooperative trial of a recombinant human interferon, interferon alfa-2a, in patients with multiple myeloma. Interferon alfa-2a showed objective antitumor effects on this type of malignancy, producing a partial remission rate of 21.3% in 47 evaluable cases.

Patients and Methods

Sixty-four multiple myeloma patients from 21 major university and cancer hospitals entered this Phase II study. There were 42 IgG; 16 IgA; 5 Bence-Jones (B-J) type; and 1 IgD. The patients' ages ranged from 39 to 84 years (median, 62 years), and included 39 males and 25 females.

Hoffmann-La Roche Inc. (Nutley, NJ), Takeda Pharmaceutical Co. Ltd. (Osaka, Japan), and Nippon Roche Co. Ltd. (Tokyo, Japan) prepared interferon alfa-2a in *Escherichia coli* through recombinant DNA technology and purified it using a monoclonal antibody immunoab-

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TABLE 1. Results of Interferon Alfa-2a Treatment in Multiple Myeloma

Type of myeloma	No. of patients	Responses				Response rate (%)	
		PR	MR	NC	PD	PR	PR + MR
IgG	31	5	2	23	1	16.4	22.5
IgA	12	4	3	5	0	33.3	58.3*
B-J	4	1	0	3	0	25.0	25.0
Total	47	10	5	31	1	21.3	31.9

* $0.05 < P < 0.1$.

PR: partial remission; MR: minor response; NC: no change; PD: progressive disease; IgG: immunoglobulin G; IgA: immunoglobulin A; B-J: Bence-Jones.

sorption column. The substance was more than 98% pure and had a specific activity of 2 to 4×10^8 U/mg of protein. Interferon alfa-2a was administered intramuscularly (IM) daily with doses escalating from 3×10^6 U to 6, 9, 18, 36, and 50×10^6 U every 3 days. Treatment was stopped when side effects made continuation difficult or when there was no improvement after at least 4 weeks of treatment. Response classification was based principally on the criteria of the Myeloma Task Force of the (US) National Cancer Institute.[9] Partial remission (PR) was defined as more than a 50% reduction of serum M-protein and/or more than a 50% reduction of urine B-J protein. Minor response (MR) consisted of a 25% to 50% reduction of serum M-protein and/or B-J protein. These responses were sustained for at least 4 weeks. No change (NC) meant M-protein remained within ±25%. A patient was considered to suffer from progressive disease (PD) when M-protein increased more than 25%, or if there was a definite deterioration of the patient's clinical condition.

Antibodies to interferon alfa-2a were tested in the patients during and after treatment. Serial two-fold dilutions of sera from the patients were incubated with an equal volume 40 IU/ml of interferon alfa-2a for 1 hour at 37°C. Interferon activity of the above mixture was assayed by a plaque reduction assay in Fogh-Lund (FL) cells using Sendvis virus as challenge according to the method described by Kohase *et al.*[10] Statistical analysis was done with the chi-square test or Student's *t* test, if indicated.

Results

Of the 64 patients registered in this study, 17 were excluded from the evaluation of response because of protocol violations: 7 patients because the preceding antitumor drugs were given within 14 days prior to interferon alfa-2a administration; 4 because of concurrent use of prednisolone; 3 because their performance status (performance status 4, Eastern Cooperative Oncology Group) was too poor for the evaluation of a new drug; and 3 because the administration period of interferon alfa-2a was less than 14 days due to severe side effects, a period considered too brief to evaluate the effect of this drug. These last three patients, however, were included in the evaluation of side effects.

The starting dose of interferon alfa-2a in evaluable patients was 3×10^6 U in 44 patients, 6×10^6 U in 2 patients, and 9×10^6 U in 1. Maximum tolerable doses were given daily unless severe side effects appeared. The maximum daily doses given were 50×10^6 U in 4 patients, 36×10^6 in 6, 25×10^6 in 1, 18×10^6 in 9, 12×10^6 in 3, 9×10^6 in 12, 6×10^6 in 8, and 3×10^6 in 4. Most of the patients given 18×10^6 U or more, however, could not tolerate the treatment for a long period because of side effects such as severe malaise, severe anorexia, and high fever; therefore, the usual maintenance daily doses were 9 or 6 $\times 10^6$ U. Treatment periods ranged from 14 to 345 days (median, 36 days). Total dosage given ranged from 72 $\times 10^6$ to 3526×10^6 U (median, 252×10^6 U).

Among 47 evaluable cases, 10 achieved PR, 5 MR, 31 NC, and 1 PD. Response rate was 21.3% and, if MR is included, 31.9% (Table 1). To achieve PR, a median of 29 days (range, 22–89 days) was required and a median total dosage of 532×10^6 U (range, 84–916×10^6 U) was given. The PR lasted for a median of 8 weeks (range, 4–55 weeks). Overall, the remission duration was rather short, although in one case it was 55 weeks and in another it was 42-plus weeks.

Although the objective responses were assessed only by the reduction of M-protein, in one previously treated IgG-k, Stage III[11] patient, serum IgG dropped from an initial value of 5520 mg/dl to below 2360 mg/dl, the erythrocyte sedimentation rate from 114 to below 20 mm H_2O, plasma cells in the bone marrow from 14.0% to 1.4%, and the red blood cells (RBC) increased from 317 $\times 10^4$ to $412 \times 10^4/mm^3$. The absolute decrease of plasma cells in the bone marrow was confirmed by repeated bone marrow aspiration. The patient had extensive osteolytic lesions in almost all his bones before the treatment. After the initiation of interferon alfa-2a, these lesions showed a gradual but definite improvement with slight recalcification after 7 months. Before interferon alfa-2a treatment, the patient was confined to bed with severe lumbar pain, which subsided gradually and disappeared almost completely 9 months after initiation of therapy. The patient became ambulatory and his remission lasted 55 weeks with maintenance interferon alfa-2a (9×10^6 U/day) therapy.

In seven other PR cases, objective and/or subjective responses were noted in addition to the reduction of serum M-protein. There was a definite reduction of plasma cells in the bone marrows of five patients (more than a 95% reduction in four, and a 50% reduction in one); disap-

pearance or decrease of pain in five patients; disappearance of a pleural mass in one patient; and more than a 25% increase in RBC in another.

The median total dosage given to PR patients was 691 $\times 10^6$ U and the median treatment period was 38 days, while for MR patients and nonresponders (NR) (NC + PD) dosage was 141 $\times 10^6$ and 228 $\times 10^6$ U for 38 and 35 days, respectively. The respective median and mean daily doses were 12.0 $\times 10^6$ and 16.0 $\times 10^6$ U in PR patients, 5.4 $\times 10^6$ and 7.0 $\times 10^6$ U in MR patients, and 7.6 $\times 10^6$ and 8.1 $\times 10^6$ U in NR patients (Table 2). Since PR patients received maintenance doses of interferon alfa-2a after achieving remission, the median daily dose in these patients until they reached remission was 14.8 $\times 10^6$ U. Thus, PR patients received higher daily doses of interferon alfa-2a. The difference of administered daily doses between PR and nonresponders was statistically significant ($P < 0.01$; Student's t test). The treatment response for each type of multiple myeloma is shown in Table 1. No particular pattern of sensitivity was noted. When MR is included, however, IgA patients tended to show a better response (58.3%) than those with IgG (25.8%) and B-J (25%) type multiple myeloma, although the difference showed only a borderline statistical significance ($0.05 < P < 0.1$; chi-square test with Yates' correction).

Thirty-nine patients had previously been treated with various chemotherapeutic regimens using one drug or a combination of 2 to 4 of the following: melphalan, prednisolone, cyclophosphamide, vincristine, doxorubicin, procarbazine and 1-(4-amino-2-methyl-5-pyrimidinyl) methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU). These patients were considered clinically refractory to these drugs because there was no improvement despite the resulting myelosuppression; eight were previously untreated. PR was obtained in 20.5% of previously treated patients and 25% of previously untreated patients.

TABLE 2. Dose of Interferon Alfa-2a in Relation to Response

Response	No. of patients	Total dosage ($\times 10^6$ U) (median)	Administered period (median)	Daily dose ($\times 10^6$ U) Median	Daily dose ($\times 10^6$ U) Mean
PR	10	691	38	12.0	16.0*
MR	5	141	38	5.4	7.0
NR (NC + PD)	32	228	35	7.6	8.1

* $P < 0.01$ *versus* NR; and not significant *versus* MR.
PR: partial remission; MR: minor response; NR: no response; NC: no change; PD: progressive disease.

Adverse Reactions

Side effects were observed in more than two-thirds of the patients (Table 3). Fever over 38°C usually accompanied by chills was noted in 58% of the patients and seemed unrelated to the doses of interferon alfa-2a. Fever was unusual after several days of treatment. Anorexia was noted in 50%, nausea and vomiting in 24%, and malaise in 20% of patients. These side effects seemed related to the doses of interferon alfa-2a and often became dose-limiting factors in some of the patients who received high doses (36 $\times 10^6$ to 50 $\times 10^6$ U). Dyspnea with cyanosis was observed in one patient after the first dose of interferon alfa-2a (3 $\times 10^6$ U), resulting in discontinuation of treatment. Mild lethargy was observed in an 80-year-old woman 14 days after the initiation of 12 $\times 10^6$ U of therapy. Delta waves were seen on the electroencephalogram; these findings became normal 20 days after the discontinuation of interferon alfa-2a. Myelosuppression was also common.

Thrombocytopenia was more marked than leukopenia; both, however, quickly returned to the pretreatment values when interferon alfa-2a was discontinued. A reduction in platelets of more than 25% was noted in 56% of patients. Leukocytes decreased by more than 25% in 38% of those treated. Platelets and leukocytes were reduced by more than 50% in 38% and 22% of treated patients, respectively. The median pretreatment platelet counts were 15 $\times 10^4$/mm^3 (range, 5.8–52.3 $\times 10^4$) and the median nadir counts were 7.8 $\times 10^4$/mm^3 (range, 2.2 $\times 10^4$–23.6 $\times 10^4$); leukocytes were 3300/mm^3 (range, 1680–8500) and 1900/mm^3 (range, 900–5800), respectively. Elevations of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were observed in 20% and 16% of patients, respectively. These were all mild elevations of less than 150 U/ml. Elevation of blood urea

TABLE 3. Side Effects of Interferon Alfa-2a Treatment

	No. of patients	(%)
Fever over 38°C	29	(58)
Anorexia	26	(52)
Nausea and vomiting	13	(26)
Malaise	10	(20)
Alopecia	2	(4)
Dyspnea with cyanosis	1	(2)
Lethargy	1	(2)
Paresthesia	1	(2)
Thrombocytopenia*		
>25%	28	(56)
>50%	19	(38)
Leukopenia*		
>25%	23	(46)
>50%	11	(22)
Elevation of SGOT/SGPT	10	(20)
Elevation of BUN	1	(2)
Proteinuria	2	(4)

* More than a 25% or 50% reduction from pretreatment values.
SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; BUN: blood urea nitrogen.

nitrogen (BUN) (from 75 to 95 mg/dl) was noted in one patient whose kidney function was impaired prior to interferon alfa-2a treatment.

Antibody to interferon alfa-2a was tested in 20 patients at 2- to 4-week intervals until 4 weeks after the discontinuation of interferon alfa-2a. A neutralizing antibody was detected in 1 of 20 patients 11 weeks after the initiation of interferon alfa-2a. No particular clinical reaction to interferon alfa-2a was observed in this patient.

Discussion

Interferon alfa-2a was found to be effective in multiple myeloma. Partial remission was obtained in 10 (21.3%) of 47 evaluable patients. When minor response was included, the total number of patients responding was 17 (31.9%). The response rate of multiple myeloma to interferon alfa-2a seems to be almost the same as that to leukocyte interferon alfa and to human fibroblastoid beta interferon. Gutterman *et al.*[6] reported that leukocyte interferon alpha produced one complete remission, two partial remissions, and three improvements among ten patients with multiple myeloma. Ezaki *et al.*[7] reported that human fibroblastoid beta interferon induced one partial remission among five patients with multiple myeloma.

Although we tried to give maximum tolerable doses of interferon alfa-2a, the longer use of the higher doses of interferon alfa-2a, such as 36×10^6 or 50×10^6 U/day, was almost intolerable to the patients due to severe malaise and anorexia. For most of the patients, 9×10^6 U of interferon alfa-2a was the maximum tolerable daily dose for longer use. Higher doses seemed to exert more effect, however, since 10 PR patients received a mean daily dose of 16.0×10^6 U, while 5 MR patients and 32 nonresponders received 7.0×10^6 and 8.0×10^6 U, respectively ($P < 0.01$). This indicated that patients who could tolerate higher doses of interferon alfa-2a, or those administered higher doses despite adverse reactions, possibly had a better chance to respond.

Adverse reactions to interferon alfa-2a included fever, anorexia, nausea and vomiting, malaise, diarrhea, thrombocytopenia, leukopenia, and liver function abnormality. Thrombocytopenia was more marked than leukopenia. Patients, however, recovered quickly after discontinuation of interferon alfa-2a. These side effects were almost the same as those reported in previous studies on interferons including interferon alfa-2a.[2-8] Except for fever, these reactions appeared related to the dose and the treatment period. Neurologic toxicity, observed in patients receiving high doses of interferon alfa-2a,[12] was seen in two patients. Symptoms included mild somnolence with treatment of 12×10^6 U/day and paresthesia of lower extremities with a dose of 9×10^6 U/day.

Melphalan—probably the most active drug for multiple myeloma—is reported to produce about a 25% to 40% response when used as a single agent.[13-15] Although the response rate in our study was not so high, interferon alfa-2a treatment definitely showed objective effects. It was effective for the patients previously treated with melphalan and other antitumor drugs who were clinically refractory to these conventional treatment modalities. Clinically, at least, no cross-resistance appears to exist between interferon and conventional antitumor agents for multiple myeloma.

The results of the present study indicate definite efficacy of interferon alfa-2a for multiple myeloma. Further study of this agent is warranted, especially in combination with other antitumor drugs.

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