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Treatment of plasma cell neoplasm with recombinant leukocyte A interferon and human lymphoblastoid interferon

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Summary. *Thirty cases of plasma cell neoplasms (24 multiple myeloma, one plasma cell leukemia, and three primary macroglobulinemia) were treated with two kinds of highly purified α-interferons, recombinant human leukocyte interferon (rIFN-αA) (16 cases) and human lymphoblastoid interferon (HLBI) (14 cases). Partial remission (PR) was obtained in two of 16 evaluable cases treated with rIFN-αA and in two of 12 evaluable cases treated with HLBI. If minor response (MR) was included, responses were observed in seven (31.3%) and six (50%), respectively. Response (PR + MR) was noted in 38% of 21 previously treated patients and 71% of seven previously untreated patients. Side-effects were noted in more than two-thirds of the patients. They included fever, malaise, nausea/anorexia and myelosuppression. Thus, these two kinds of highly purified α-interferon were effective in plama cell neoplasm, producing unequivocal response in 14.3% of the cases without unacceptable side-effects.*

Introduction

In addition to antiviral activity, interferon is known to possess antitumor activities against spontaneous and transplantable animal tumors of both viral and nonviral origins [5]. Recently human interferons have been shown to possess antitumor properties against various human malignancies, including osteogenic sarcoma, malignant lymphoma, multiple myeloma, leukemia, breast cancer, and renal cell carcinoma [2, 4, 6–8, 10, 11]. Although the true biological function of interferon in human malignancy remains largely speculative, interferon seems to possess both a direct cytotoxic effect on tumor cells and an indirect effect mediated through immune systems [5].

We report here our clinical experience with two kinds of interferons, recombinant human leukocyte A interferon (rIFN-αA) and human lymphoblastoid interferon (HLBI), in 30 patients with plasma cell neoplasm. Both interferons showed objective antitumor effects against this type of malignant tumor.

Patients and methods

Thirty cases of plasma cell neoplasms were treated with either rIFN-αA (16 cases) or HLBI (14 cases) in nonrandomized phase II studies at Nagoya University Hospital and its affiliated hospitals. There were 14 cases of multiple myeloma (9 IgG, 2 IgA, and 3 Bence-Jones (B-J) type), one plasma cell leukemia (IgG), and one primary macroglobulinemia in the rIFN-αA group, and 12 cases of multiple myeloma (8 IgG, 2 IgA, 1 B-J type, and 1 IgD) and two primary macroglobulinemia in the HLBI group. Patients' ages ranged from 48 to 71 years, with a median of 60, in the rIFN-αA group, and from 48 to 80, with a median age of 61, in the HLBI group. There were 11 male and five female patients in the rIFN-αA group and eight male and six female patients in the HLBI group.

rIFN-αA was prepared by recombinant DNA technology by Hoffman-LaRoche, Inc., Nutley, NJ, and Takeda Pharmaceutical Co. Ltd, Osaka, and was purified using a monoclonal antibody immunoabsorption column. It had a specific activity of $2-4 \times 10^8$ IU/mg protein. rIFN-αA was administered IM daily, with doses escalating every 3 days from 3×10^6 U to $6\times$, $9\times$, $18\times$, $36\times$, and 50×10^6 U. The starting dose was 3×10^6 U in 11 patients and 6×10^6 U in five patients. Maximum tolerable doses were given daily unless severe side-effects appeared. Maximum tolerable doses were 50×10^6 U in three patients, 36×10^6 in three, 18×10^6 in six, and 9×10^6 in four. However, none of the patients was able to tolerate 18×10^6 or more for a very long period, because of side-effects such as severe malaise, severe anorexia and high fever, and the usual daily maintenance doses were therefore 9×10^6 or 6×10^6 U. The treatment period ranged from 10 to 363 days,with a median of 43 days. The total doses given ranged from $99-3{,}706 \times 10^6$ U, with a median of 425×10^6 U.

HLBI was prepared by Wellcome Research Laboratories, Beckenham, Kent, from Sendai virus-induced cultures of human Namalwa cells and was purified in part by means of an anti-interferon antibody affinity system. It had a specific activity of $1-2 \times 10^8$ IU/mg protein. Since the supply of HLBI was rather limited, the doses were not escalated as in the case of rIFN-αA and 3×10^6 or 6×10^6 U were given IM. The latter doses were usually given if patients could tolerate them. In two cases of HLBI, 3×10^6 U/day, was discontinued after 1 and 9 days because of patient refusal owing to the side-effects. These two cases were excluded from the evaluation of response but included in the evaluation of side-effects. In 12 further cases, the treatment period ranged from 14 to 74 days, with a median of 41 days. Total doses given ranged from $42-342 \times 10^6$ U, with a median of 121×10^6 U.

Treatment was discontinued when the side-effects made continuation difficult or when there was no improvement of the disease after at least 4 weeks of treatment. Response was

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classified as follows: partial response (PR) if there was more than 50% reduction of serum M protein and/or disappearance of urine B-J protein; and minor response (MR) if there was 25%–50% reduction of serum M protein and/or urine B-J protein. The above response should be sustained for at least 4 weeks. No change (NC) was recorded when M protein did not change by more than 25% from the original value; and progressive disease (PD) if M protein increased by more than 25% or there was a definite deterioration of the clinical condition.

Results

Among 16 evaluable cases treated with rIFN-αA, two showed PR, five MR, eight NC, and one PD. The response rate was 12.5% or, if MR is included, 43.8%. Among 12 evaluable cases treated with HLBI, two showed PR, four MR, five NC, and one PD. The response rate was 16.7% or if MR was included, 50%. In all, the response rate was 14.3%, or 46.4% if MR is included (Table 1).

In the rIFN-αA group, the median total dose given for responders (PR + MR) was 573×10^6 U and the median treatment period was 35 days, while the corresponding data for nonresponders (NC + PD) were 336×10^6 U and 44 days, respectively. Thus, responders received higher doses of rIFN-αA per day. In the HLBI group, the median total dose for responders was 124×10^6 U and the median treatment period was 31 days, while the corresponding data for nonresponders were 198×10^6 U and 42 days, respectively. The response according to the type of plasma cell neoplasms is shown in Table 2. No particular pattern of sensitivity was noted.

Twenty-one patients (14 in rIFN-αA and 7 in HLBI) had previously been treated with various chemotherapeutic regimens with single drugs or combinations of two to four drugs selected from melphalan, prednisolone, cyclophosphamide, vincristine, adriamycin, procarbazine, and 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU), and had been considered clinically refractory to these drugs, mainly because no improvement of the diseases was observed in spite of the resultant myelosuppression. Seven (3 in rIFN-αA and 4 in HLBI) patients had received no previous treatment. Response (PR + MR) was noted in 38% of the previously treated patients and 71% of the previously untreated patients (Table 3). Since the number of the latter group was very small, the difference was not statistically significant by the χ^2-test.

One of the two cases classified as PR following rIFN-αA treatment was a 48-year-old man with IgG-k multiple myeloma stage III [3], who had previously been treated with cyclophosphamide, melphalan, and prednisolone. Eight weeks after the last chemotherapy, rIFN-αA was started on 11 August 1982 with 3×10^6 U daily, which was escalated at 3-day intervals through 6 ×, 9 ×, 18 ×, and 36 × to 50×10^6 U. Treatment with 50×10^6 was discontinued after 5 days on 30 August due to fever, anorexia, and severe malaise, and resumed with 9×10^6 U on 3 September; the dosage was increased to 18×10^6 on 7 September, wich was continued till 22 September. After this date, the patient was given 9×10^6 U daily until he was discharged from the hospital in June 1983. At the end of September, his serum IgG dropped from the initial value of 5,520 mg/dl to below 3,000 mg/dl, ESR from 114 to below 40 mm H_2O, total protein from 9.4 to 6.8 g/dl, and plasma cells in the bone marrow from 14.0% to 1.4%. While rIFN-αA treatment continued, his IgG dropped to

Table 1. Treatment of plasma cell neoplasm with interferons

	rIFN-αA	HLBI
Entered	16	14
Evaluable	16	12
Partial response (PR)	2	2
Minor response (MR)	5	4
No change (NC)	8	5
Progressive disease (PD)	1	1
PR	12.5%	16.7%
PR + MR	46.8%	50.0%
Period to PR (weeks)	2, 4	2, 4
PR duration (months)	1, 11	1, 15

Table 2. Response to interferons related to type of plasma cell neoplasm

	PR	MR	NC + PD	Total
Multiple myeloma	3	8	13	24
IgG	1	5	9	15
IgA	1	2	1	4
IgD	0	0	1	1
B-J	1	1	2	4
Plasma cell leukemia	0	0	1	1
Primary macroglobulinemia	1	1	1	3
Total	4 (14.3%)	9 (32.1%)	15 (53.6%)	28

Table 3. Response to interferons related to previous treatment in plasma cell neoplasm

Previous treatment	No. of cases	PR	MR	NC + PD	% of PR + MR
Treated[a]	21	2	6	13	38.1
Untreated	7	0	2	2	71.4

[a] Treated with one or with combinations of two to four drugs selected from melphalan, prednisolone, cyclophosphamide, vincristine, adriamycin, procarbazine and 1-(4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU)

Table 4. Side-effects of interferon therapy in plasma cell neoplasm

Side-effect	rIFN-αA (%)	HLBI (%)
Fever	69	57
Nausea/anorexia	38	21
Malaise	13	14
Diarrhea	13	0
Skin eruption	0	14
Thrombocytopenia[a]	50	29
Leukopenia[a]	38	36
Increase of GPT	6	21
Increase of BUN	6	0

[a] More than 25% decrease from pretreatment values

2,360 mg/dl, ESR to 20 mm H_2O, and total protein to 6.4 g/dl. RBC increased from 317×10^4 to $412 \times 10^4/cm^3$, WBC and platelets recovered to above $4,500/cm^3$ and $15 \times 10^4/cm^3$, respectively, and the response was classified as PR in November, 1982. The absolute decrease of plasma cells in the bone marrow was confirmed by repeated bone marrow aspirations. He had extensive osteolytic lesions in almost all his bones. They showed a gradual but definite improvement with slight recalcification in February 1983. Before rIFN-αA treatment he was confined to bed due to severe lumbago; this subsided gradually and he started to walk in spring 1983. The lumbago disappeared almost completely in May and he was treated as an outpatient after his discharge on 11 June 1983. After his discharge he received 9×10^6 U of rIFN-αA at the outpatient clinic twice weekly until 13 August 1983, when the serum IgG was found to have increased above 3,000 mg/dl. Therefore, rIFN-αA (9×10^6 U) was given daily except on Sunday. IgG showed slight decrease. However, IgG became 4,350 mg/dl on 11 November, when the level of plasma cells in the bone marrow was found to be 37.8% and rIFN-αA was discontinued. He received $3,700 \times 10^6$ U rIFN-αA during the 15 months without any unacceptable side-effects. His remission lasted 11 months. The other PR case following rIFN-αA was a 57-year-old female patient with previously untreated B-J type myeloma, stage III. She received $3-50 \times 10^6$ U daily for 28 days. rIFN-αA was discontinued because of severe malaise and anorexia with abnormal liver function tests. Two weeks after the initiation of rIFN-αA, urinary B-J protein disappeared and plasma cells in the bone marrow decreased from 17.6% to 7.6%. The remission lasted only 1 month.

One PR following HLBI occurred in a 64-year-old woman with IgA-k myeloma refractory to melphalan and prednisolone, who received 3×10^6 U of HLBI daily for 3 weeks and 6×10^6 three times a week thereafter for 9 weeks. Serum IgA decreased from 1,500 to 500 mg/dl, and plasma cells in the bone marrow decreased from 10.0% to 5.0%. She maintained PR for 15 months with only occasional HLBI injections. Another PR following HLBI was in a 72-year-old man with previously untreated primary macroglobulinemia (IgM-k), who received 3×10^6 U of HLBI daily for 42 days. Two weeks after the initiation his IgM decreased from 5,400 to 2,600 mg/dl, and it was 2,280 mg/dl at 4 weeks. His remission, however, lasted only 1 month.

Side-effects were noted in more than two-thirds of the patients (Table 4). Two patients refused further treatment of HLBI because of severe chills and fever and severe malaise. Fever over 38° C was noted in 69% of the rIFN-αA group and 57% of the HLBI group. This was usually accompanied by chills, and seemed to be unrelated to the doses of interferons. Fever became uncommon after several days' treatment. Nausea/anorexia was noted in 38% of the former group and in 21% of the latter, and malaise in 13% and 14%, respectively. These side-effects seemed to be related to the doses of interferons and often became dose-limiting factors in some of the patients who received high doses ($36-50 \times 10^6$ U) of rIFN-αA. Skin eruption was seen in two patients who received HLBI. Myelosupression was also common. It was mild and reversible when interferons were discontinued, however. More than 50% decrease of platelets was noted in 50% of the rIFN-αA group and 29% of the HLBI group. More than 50% decrease of leukocytes was observed in 38% and 36%, respectively. Mild liver function abnormality was noted in 6% of the rIFN-αA group and in 21% of the HLBI group. Kidney function abnormality was noted in one case in the rIFN-αA group, but it seemed to be related rather to the disease itself, being a massive excretion of urinary B-J protein.

Discussion

The two kinds of highly purified α-interferons, recombinant A interferon (rIFN-αA) and a mixture of natural α-interferons from Namalwa cells (HLBI), were found to be effective for plasma cell neoplasms. Responses were obtained in two of 16 evaluable cases treated with rIFN-αA and two of 12 evaluable cases treated with HLBI. If minor response is included responses were observed in seven cases (31.3%) and six cases (50%), respectively.

The response rate of plasma cell neoplasms to these interferons seems to be almost the same as that to leukocyte α-interferon and human fibloblastoid β-interferon. Gutterman et al. reported that leukocyte α-interferon produced one CR, two PRs, and three improvements among 10 patients with multiple myeloma [6]. Ezaki et al. reported that human fibroblastoid β-interferon induced one PR among five patients with multiple myeloma [4].

We adopted the different treatment schedules for the two interferons mainly because the supply of recombinant interferon was sufficient to give maximum tolerated doses, while that of HLBI was rather limited. However, the longer use of the higher doses of rIFN-αA, such as 36×10^6 or 50×10^6 U/day were almost intolerable for all patients, due to severe malaise and anorexia. For most of the patients, 9×10^6 U of rIFN-αA was the maximum tolerable daily dose over any substantial period of time.

As for rIFN-αA, however, higher doses seemed to exert a more pronounced effect, since seven responders (PR + MR) received a median total dose of 573×10^6 U during 35 days (median), while nine nonresponders received 336×10^6 U during 44 days. A calculated median daily dose (median total dose/median treatment period) was 16×10^6 U in responders and 7.6×10^6 U in nonresponders. This indicated that patients who could tolerate higher doses of rIFN-αA possibly had a better chance of responding. As for HLBI, there was no difference in response between the groups that received $3 \times$ and 6×10^6 U daily. Since the number of patients studied was very small any altempt at a definite conclusion would be premature, but the clinical effect seemed to be the same in both groups in spite of the different doses administered. This might be because rIFN-αA is a recombinant interferon consisting of only one subtype of α-interferon while HLBI is a mixture of several subtypes of natural α-interferon, or because the serum concentration after IM injection of rIFN-αA was significantly lower than after the same dose of natural α-interferon [7].

The side-effects of the interferons included fever, nausea/anorexia, malaise, diarrhea, skin eruption, thrombocytopenia, leukopenia, and liver function abnormality. These side-effects were almost the same as those reported in previous studies on interferons including HLBI and rIFN-αA [2, 4, 6–8, 10, 11]. Skin eruption was noted only in the HLBI group. Except for fever and possibly skin eruption, the side-effects seemed to be related to the doses and the treatment period. Therefore, side-effects were noted more frequently in the rIFN-αA group, since the median total dose of rIFN-αA was 425×10^6 U and that of HLBI was 121×10^6 U.

Melphalan, probably the most active drug for plasma cell neoplasms, is reported to produce about 25%–40% of response when used as a single agent [1, 9]. Although the

response rate to the interferons in our study was lower than those figures, these interferons definitely had objective effects. It was effective in the patients who had been treated with melphalan and other antitumor drugs and had become clinically refractory to these conventionally available drugs. Therefore, at least clinically, there seemed to be no cross-resistance between interferons and conventional antitumor agents for plasma cell neoplasms. If interferon is used for previously untreated cases the response might be higher, as we have observed in the present study.

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