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Lack of response in nine patients with breast cancer treated with fibroblast interferon*

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Summary. *Nine patients with metastatic breast cancer were treated with a minimum of 6×10^6 U/day of β-interferon (IFN-β) for at least 6 weeks. In patients whose disease did not progress during this period treatment was continued to a maximum of 13 weeks, while in other patients doses were escalated. With daily treatments over 3 weeks the maximum tolerated dose was found to be around 60×10^6 U/day.*

Fever occurred regularly. The dose-limiting toxicities were granulocytopenia and increasing liver enzymes.

No objective remissions were observed. One patient showed stable disease after her cancer en cuirasse had rapidly progressed under chemotherapy.

One patient each with nasopharyngeal carcinoma and fibrous sarcoma were also treated without success.

IFN-β at this moderately toxic dose given over a period of 6–13 weeks is of no clinical value in the treatment of metastatic breast cancer in women.

Interferons (IFN) from different cells – leukocytes, fibroblasts, or lymphoblasts – are known to have antitumor activity in animal tumors [6–8, 17]. There is also no longer any question that they are potentially effective agents against human tumors. Future studies will have to show whether this antitumor effect can be exploited in the treatment of some malignancies. One of the many unanswered questions is the choice of the interferon type to be used in clinical cancer trials. α-Interferon (IFN-α) from leukocytes has now been under tests for some years, whereas β-interferon (IFN-β) from fibroblasts has been only sporadically tried in patients with measurable malignant disease. Immune interferon (IFN-γ) from lymphoblasts has only recently become available for clinical trials, and phase II data are now being generated.

There is no scientific reason for the preferred use of IFN-α in cancer trials, but the way interferons are being tested in man is largely dictated by the limited supply of the material and the sources available to the different investigators. The biological differences in the three classes of interferons are large enough to demand separate investigations of their efficacy. The different interferons may prove to have varying effects depending on the type of tumor treated [4]. It is also possible that cooperation between two or more interferons is required to achieve biological activity.

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We here present our data on 11 patients (breast cancer, 9; fibrosarcoma, 1; and lymphoepidermoid carcinoma of the nasopharynx, 1) treated with fibroblast interferon for 6–13 weeks.

Materials and methods

Interferon preparation. Human IFN-β was obtained from the pharmaceutical company of Rentschler & Co./Germany. It is prepared from cultured diploid fibroblasts by stimulation with polyI · polyC by the technique of superinduction [10, 18]. The specific activity was 10^6 U/mg protein, i.e., 0.2 μg IFN/mg. It was stored as a lyophilized powder at −20° C and dissolved immediately before its administration.

Patient selection. Only patients with clearly measurable disease for whom no conventional therapy was available were entered into the study. Life expectancy was above 3 months, performance status was 2 or better according to the WHO scale. Only patients with good liver and renal function were included. All patients were informed about the experimental nature of the planned treatment and gave informed consent.

Nine patients had mammary carcinoma, and the sites of metastases are given in Table 1. One patient suffered from pulmonary metastases of a fibrous sarcoma. A 60-year-old man was treated for nasopharyngeal carcinoma with far-advanced local disease that had recurred after repeated courses of radio- and chemotherapy. All patients had had intensive prior chemotherapy, which had been discontinued because of progressive disease at least 4 weeks before institution of the IFN treatment.

Physical examination, ECG, and extensive laboratory studies including complete blood count, renal and liver function tests, serum calcium, protein electrophoresis, uric acid level, and urinalysis were done prior to the treatment and repeated at weekly or biweekly intervals. Tumor parameters were checked weekly if clinically evaluable, or every 3 weeks by X-ray studies.

Treatment. Interferon was dissolved in 250 ml 5% Gl/W and infused daily over 30 min. For the first week and later with each dose escalation, pulse rate, blood pressure, and temperature were closely monitored. The initial patients received reduced doses of IFN for the first few days to test for individual intolerance. Thereafter all patients were given a minimum of 6×10^6 U/day for at least 6 weeks. This schedule was chosen

Table 1. Diagnosis and treatment of the 11 patients treated with IFN-β

Pat. no. Age/sex	Primary tumor/ type of metastases	Dose[a] of IFN-β/ duration of therapy at each dose level	Granulocyte nadir	Max. yGT (normal < 28)	Performance scale[b] before/after change in body weight
1 58/Female	Breast cancer/ chest wall, lung, bone	6 MU/42 days	1,900	355	2/3 − 2 kg
2 44/Female	Breast cancer/ chest wall, lung	6 MU/42 days	2,600	238	1/1 − 3 kg
3 44/Female	Breast cancer/ chest wall	6 MU/31 days 12 MU/ 2 days 18 MU/22 days	1,300 2,100	175	1/3 − 4 kg
4 66/Female	Breast cancer/ chest wall, bone	6 MU/28 days 16 MU q 3 days × 4	840	24	0/1 + 1.5 kg
5 42/Female	Breast cancer/ chest wall	6 MU/ 2 days 12 MU/ 2 days 24 MU/ 2 days 48 MU/ 2 days 60 MU/20 days 6 MU q 3 days × 5	 1,500 750	 800	0/0 − 1 Kg
6 66/Female	Breast cancer/ lung, pleura, bone	6 MU/42 days 6 MU q 3 days × 6	2,100	88	1/3 + 1.5 kg
7 52/Female	Breast cancer/ lung, pleura	6 MU/42 days	1,000	82	0/2 − 1 kg
8 45/Female	Breast cancer/ lung	6 MU/42 days	3,300	180	1/2 − 1.5 kg
9 47/Female	Breast cancer/ chest wall, bone	6.6 MU/91 days (Cimetidin 1 g/day/7 weeks)	1,000	186	1/2 − 4 kg[c]
10 43/Female	Fibrous sarcoma/ lung	6 MU/21 days 12 MU/10 days 15 MU/10 days	900 950	22	0/1 − 2.5 kg
11 68/Male	Nasopharyngeal camer local	6 MU/38 days	9,000	179	2/2 − 2.5 kg

[a] 1 MU: 1×10^6 U
[b] WHO scale
[c] Hip replacement during IFN therapy

because Treuner's group [14, 16], using IFN-β from the same source, had observed a dramatic complete remission with 4×10^6 U/day in a 16-year-old boy with far advanced nasopharyngeal carcinoma. The onset of response was seen 3–4 weeks after start of therapy.

In three of our patients (nos. 3, 6, 9) in whom there was no clear progression of disease during the first 6 weeks IFN treatment was continued. The longest therapy lasted 13 weeks. To check whether higher doses were more effective and tolerated for prolonged periods, doses were escalated in three patients. One woman received a maximum daily dose of 60×10^6 U for 20 days. The length of treatment at different dose levels and the total amounts of IFN administered are given in Table 1.

Toxicity. All patients experienced febrile reactions with chills after IFN administration. The maximum temperature was reached about 2 h after the end of the infusion, with normalization after another 2–3 h. In patients treated with increasing doses of IFN the elevation in temperature was clearly dose-related. The highest recorded temperature was 39.4° C. The febrile reactions were promptly relieved or were prevented by phenacetin or metamizol.

The major toxicity was granulocytopenia. The nadir was seen between days 2 and 7, with no further drop in spite of continued therapy. The degree of leukopenia during treatment at 6×10^6 U/day was variable (Table 1). In four of the 11 patients nadir values of 1,000 granulocytes or below were recorded, whereas four patients never had a nadir, their leukocytes staying above 4,000/μl. Patient no. 5 had prolonged leukopenia, with a second nadir of 750 granulocytes when the dose was escalated. There was never any sign of infection. Leucopenia was quickly reversible in all patients within 3–4 days after discontinuation of IFN therapy. No patient remained leukopenic during intermittent treatment with IFN given every third day.

The counts of blood lymphocytes, monocytes, eosinophilic granulocytes, and thrombocytes were not consistently altered. The reticulocyte count never dropped appreciably but the average hemoglobin fell by about 2 g over the total treatment period. It is not certain whether this decrease was due to the treatment or to the underlying malignant disease.

Table 2. Therapeutic results with IFN-β in human cancer as reported by other workers

Diagnosis	Dose of IFN-β and schedule	Therapeutic effect	
Breast cancer	6×10^6 U IM every 5 days for 6 weeks	11 Patients, regression of some skin nodules	[15]
	$3-6 \times 10^6$ U/day for 1 month	3/6 Partial remissions 1 minor response (< 50%)	[1]
	3.3×10^6 U twice weekly	1/1 Partial remission	[1]
Non-Hodgkin's lymphoma, low-grade malignancy	4.5×10^6 U/day for 4 weeks, increased to 9×10^6 U/day for 2 weeks	4/10 Stable disease, 1 partial regression	[5]
Malignant lymphoma, histological type unknown	$1.5-6 \times 10^6$ U/day for 8–30 days	8/8 Progressions	[1]
Multiple myeloma	$1-5 \times 10^6$ U/day for 2–4 weeks	8/8 Progressions	[13]
Neuroblastoma, stage IV, age < 1 year	0.5×10^6 U/day for 21 days, than 3 times weekly for 32 weeks	73 Children randomized study of chemotherapy + IFN-β, no difference in survival	Deutsche Gruppe für pädiatrische Onkologie, and personal communication [12]
Nasopharyngeal carcinoma	4×10^6 U/day for 5 weeks, followed by 3 times weekly	6 Children: 1 complete remission; 2 stable for 4 and 8 months; 2 progressions; 1 withdrawal due to toxicity	[14, 16]
	10^5 U/kg 3 times weekly	1/3 Partial remission (adults)	R. Mertens (personal communication)
Osteogenic sarcoma	10^5 U/kg	106 Children, adjuv. chemotherapy ± IFN: no difference in survival	[19]

The gammaglutamyltranspeptidase (γ-GT) increased in nine of the 11 patients (Table 1). Patient 5 again showed the most pronounced change. Her alkaline phosphatase also rose to 870 U (normal < 240 U), and SGOT and SGPT rose to 89 and 105 U. No other patient had an elevation of the transaminases due to the treatment. All other laboratory values remained unchanged.

Fatigue and asthenia were frequently described with IFN. As all our patients showed progressive disease it is difficult to differentiate whether these symptoms were due to the treatment or to the disease. Patient 5 undoubtedly exhibited mild general malaise during the high-dose treatment with recovery after cessation of therapy.

With daily IV administration of β-IFN over several weeks 60×10^6 U can probably be considered as the maximum tolerated dose for good-risk patients.

Results

None of the 11 patients had an objective response to the β-IFN treatment.

Our last breast cancer patient (no. 9) had a rapidly progressive cancer en cuirasse while receiving combination chemotherapy. She showed no further progression during the treatment. Therapy was therefore continued for another 7 weeks to ensure that no late effect of the drug would be missed. Since a possibly beneficial effect of the combination of IFN with cimetidin has been reported [3, 11] this drug (1 g/day) was added for the last 7 weeks. Again the cutaneous metastases remained unchanged but she developed hypercalcemia, which was probably related to progression of her bone metastases. In this patient it is rather likely that the treatment with IFN-β had slowed the progression of disease.

Discussion

Interferons have demonstrated antitumor activity in vitro in several animal systems, and in some studies in humans. Most of the experience in man was gained from treatment with IFN-α. Observations about the effects of IFN-β are scanty (Table 2). On the other hand, in vitro experiments showed definite differences in the antitumor effect of IFN-α and -β in human tumor cell lines [4]. Therefore seemed necessary to study the activity of IFN-β in humans. Breast cancer was chosen as there have been several reports of the effectiveness of IFN-α in this type of tumor [1, 2, 9].

For several reasons we decided not to perform a classic phase-I study. IFN-β was available in only limited amounts; IFN most probably does not exert its antitumor effect by way of its antiproliferative activity but has to be regarded as a biological response modifier. The dose to be given is therefore difficult to determine and it may be much lower than the maximum tolerated dose. Also, it may be necessary to give the drug for prolonged periods and it seemed more important to define the tolerance of such long-term treatment than to define the acute single-dose toxicity. Finally, with the same IFN used in this study a dramatic complete remission of a nasopharyngeal carcinoma had been observed by others with a dose of 4×10^6 U/day. Onset of response was seen 3–4 weeks after the initiation of therapy.

Therefore we designed our protocol as a disease-oriented phase-II trial, attempting at the same time to obtain infor-

mation in individual patients on the maximum tolerated dose during prolonged treatment.

All patients received a minimum of 5×10^6 U IFN-β for 6 weeks. This dose produced definite but tolerable toxicity. 60×10^6 U/day may be close to the maximum tolerated dose for good-risk patients. Granulocytopenia, liver toxicity, and malaise were the dose-limiting side-effects.

No tumor regression was seen in our study. With nine breast cancer patients entered, the likelihood of a response rate of at least 30% is below 5% for this disease. In view of the inconveniences to the patients (side-effects, daily parenteral application) and the costs of this therapy the study was closed.

IFN-β at this moderately toxic dose given over a period 6–13 weeks is of no clinical value in the treatment of metastatic breast cancer in women.

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