Clinical Phase II Trial of Recombinant DNA Interferon (Interferon Alfa 2b) in Patients With Metastatic Malignant Melanoma

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Twenty-four patients with histologically proven metastatic malignant melanoma were included in a Phase II trial of human DNA recombinant interferon (rDNA IFNα2). They were given 10×10^6 IU of IFNα2 subcutaneously three times a week until progression of disease or major intolerance developed. Twenty-two patients were evaluable for toxicity and response. General manifestations of intolerance were seen in all the patients. Hematologic toxicity was seen in six patients and therapy had to be interrupted in one patient. Mild liver toxicity was seen in most patients after 2 weeks of treatment. These manifestations disappeared within 2 weeks after treatment was discontinued. A partial response was seen in four cases lasting 2, 4, 4, and 5 months, respectively. There were two complete responses (one skin, one lymph node metastasis) lasting 20 and 6 weeks, respectively. These results indicate a potential role for rDNA IFNα2 in treating patients with metastatic malignant melanoma. However, further trials are required to determine the optimal dose and schedule of administration and modalities of combination.

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CONVENTIONAL CHEMOTHERAPY for human metastatic malignant melanoma (HMMM) provides very poor results, with a response rate of 21% for DTIC (diethyl-triazene-imidazole-carboxamide) and only a 5% rate of complete response.[1,2] Combinations of drugs usually increase toxicity without any obvious benefit in response rate or response duration.[3–5] Because of the poor prognosis of patients with HMMM treated according to conventional medical approaches, new trials of biological response modifiers including interferons were activated. Although the specific mechanism supporting the antitumoral effect of interferons has not been clearly demonstrated, their immunomodulatory properties, their antiproliferative characteristics, and their ability of induction differentiation have generally been more precisely defined. Considering these conditions, interferons might be of clinical interest in the treatment of HMMM. Evidence of the potential activity of interferons in the treatment of malignant tumors was suggested by *in vitro* experiments[6] and, more recently, by Phase I trials.[7,8]

Patients and Methods

Patients

Twenty-four patients were included in a Phase II trial of human recombinant DNA interferon (rDNA IFNα2). All patients had histologically proven and measurable metastatic disease; no specific therapy (chemotherapy, radiotherapy, immunotherapy or hormonotherapy) was applied within the 4 weeks before a patient was entered into the study.

Criteria for participation included: life expectancy of at least 4 months; performance status not worse than Grade 2 on the Eastern Cooperative Oncology Group (ECOG) scale; no persisting toxic symptom of prior therapy; no acute illness; adequate renal, hepatic and hematologic functions (neutrophil count $> 1500/\mu$l, platelet count $> 100{,}000/\mu$l); no brain metastases suspected (a preliminary computed tomography [CT] scan was systematically performed after two patients showed evidence of brain localization within the first 2 weeks of treatment); no prior treatment with interferon (IFN) (concomitant steroids, salicylates and nonsteroid antiinflammatory agents might be used only when absolutely necessary).

Twenty-two patients were evaluable; two had to be

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TABLE 1. Patient Characteristics

No. of patients	22
Dose (induction)	10×10^6 3 times/wk
Age (yr)	
Range	34–75
Median	51
No. M/F	9/13
Disease free interval (mo)	
Range	0–60
Median	10
ECOG PS (0, 1, 2, 3)	12-6-4-0
Prior chemotherapy	
None	11
Adjuvant	2
For metastases	9
No. of courses of IFN (wk)	
Range	5–32
Median	9
No. of sites	
Range	1–2
Median	1
Dominant site	
Soft tissue	13
Bone	1
Visceral	8

ECOG PS: Eastern Cooperative Oncology Group protocols; IFN: interferon.

withdrawn from the study because of clinical evidence of brain and meningeal localization within the first 2 weeks of treatment. There were 9 men and 13 women with a median age of 51 years (range, 34–75 years). The mean disease-free interval was 10 months (range, 0–60 months). Eleven patients had never received any specific medical treatment; two patients had received adjuvant chemotherapy with DTIC; and nine patients had received different combinations of drugs for metastatic disease. All patients showed evidence of progressive disease when included in the trial.

Dominant metastatic sites were soft tissue (including skin), subcutaneous tissue and lymph nodes (13 patients), visceral (8 patients), and bone (1 patient). Nineteen patients presented with only one metastatic site and three patients presented with two metastatic sites. The primary tumor site developed on skin in 19 patients and on the choroid in 3 patients. ECOG performance scores were 0 (12 patients), 1 (6 patients) and 2 (4 patients).

TABLE 2. Clinical Toxicity

Fatigue	22
Anorexia	22
Flu-like syndrome	20
Confusion	0
Weight loss	15
Range (kg)	0–5
Median (kg)	−1

Treatment

Recombinant DNA interferon (rDNA IFNα2) was supplied by Schering Plough Corporation. The rDNA IFNα2 was injected subcutaneously at the dose of 10×10^6 IU three times a week until disease progression or major intolerance. Before initiating the treatment, patients underwent a complete physical examination and had a chest roentgenogram, electrocardiogram, and liver ultrasonography. Hematologic, chemical and urinary parameters were obtained, and screening was done for IFN neutralizing factors.

Tumor measurements were performed at baseline and then monthly; laboratory tests were repeated weekly during the first month of treatment and then every four weeks if tolerance was good. Response was defined using conventional criteria: complete response was defined as the absence of any measurable disease; partial response was defined as a greater than 50% decrease in the product of the longest perpendicular diameters of the most clearly measurable lesions without appearance of new lesions or symptomatic deterioration; stable disease was defined as a less than 25% increase in the product of any indicator lesion and a less than 50% decrease in the product of any indicator lesion without appearance of new lesions. Progressive disease was defined as a greater than 25% increase in the product of any indicator lesion and/or the development of new lesions. Patient characteristics are presented in Table 1.

Clinical Toxicity

Clinical toxicity of the treatment is shown in Table 2.[5] A flu-like syndrome affected 20 of 22 patients, although it was often prevented or decreased in severity by acetaminophen. The symptoms included fever, chills, sweats, myalgia, arthralgia, and backpain. Its severity decreased after a few weeks of treatment. Fatigue was moderate to severe, affecting all patients and persisting as long as the treatment was applied. In one case of severe fatigue (Grade 3), it disappeared after treatment was stopped, but reappeared as soon as IFN treatment was resumed.

Anorexia was noted in all patients (most of the time selectively for meat), and can be considered the major cause of weight loss observed in most patients (15 patients). Weight loss ranged from 1 to 5 kilograms and was exclusively observed during the first month of therapy.

A certain degree of anosmia and dry mouth was usual. No cardiac, renal, or neurologic toxicity occurred; nevertheless, an intense fatigue, sometimes confining to

adynamia, was usual even though no real confusion was observed.

Two patients presented with cutaneous modifications. One had erythema at the injection site lasting three days without any other symptom, and it appeared after 6 months of treatment and recurred until IFN treatment was stopped. The second patient presented with a generalized pruritic macular erythema. The erythema was observed after 8 months of treatment, and it slowly abated within two months despite ongoing therapy. No biologic or clinical toxicities other than the ones usually observed were noted for these two patients who were the two complete responders.

TABLE 3. Biological Toxicity

Blood count		
WBC	$<1.8 \times 10^3/mm^3$	4
Platelets	$<60 \times 10^3/mm^3$	2
Liver enzymes		
SGOT	>50 IU	14 (63.6%)
Alkaline phosphatase	>105 IU	15 (58.2%)
Response		
CR + PR	6	
Stable disease	0	
Progressive disease	16	

WBC: leukocyte; SGOT: serum glutamic oxaloacetic transaminase; CR: complete response; PR: partial response.

Biological Toxicity

Observed biological toxicity of the treatment is shown in Table 3.[5] Hematologic alterations were noticed in five cases. In four patients, the leukocyte count (WBC) was lower than $1.8 \times 10^3/\mu/l$, and in two patients, the platelet count was lower than $60 \times 10^3/\mu/l$. One patient presented with both disorders, and this toxic effect could not be related to previous therapies. In all cases hematologic toxicity was asymptomatic, and transient: it completely reversed within 1 or 2 weeks after treatment was stopped or the dose was decreased.

Liver enzymes were increased, unrelated to liver involvement, in most patients, mostly in a moderate way, without any clinical manifestation. The normalization of enzyme levels was spontaneously achieved in most cases as treatment was applied. In other cases, moderate liver enzyme elevation persisted and normalized within the 2 weeks after treatment was stopped.

Systematic assays for an IFN-neutralizing factor were repeated at monthly intervals, but the presence of anti-IFN-antibodies was never demonstrated.

Results

The number of courses of IFN varied, with a median of 9 weeks and a range from 5 to 52 weeks. We observed six responses among 22 patients (27%): two were complete responses (9%) and four were partial responses (18%). Five of the six responses occurred in soft tissue sites of limited size.

Regressions occurred within 1 month of starting the treatment in the two complete responders. Complete responses were observed after 32 and 40 weeks, respectively, of treatment, and lasted for 20 and 6 weeks, respectively. The sites of metastases were: one, axillary lymph nodes and one, subcutaneous tissue. The sites of relapse were the ipsilateral infraclavicular lymph nodes and the brain.

Partial responses were observed within the first (one patient) or second (three patients) month of treatment. Response duration was, respectively, 8, 12, 12, and 20 weeks. The metastatic site was soft tissue for all but one patient, and was slowly progressive. Neither of the two complete responders had received prior chemotherapy; three of the four partial responders had received prior chemotherapy without any benefit.

Discussion

In this Phase II trial of recombinant DNA Interferon $\alpha 2$ (interferon alfa 2b) in HMMM, we observed 6 objective regressions among 22 patients (response rate, 27%). We noticed prominent activity when metastases were of small size and confined to skin and lymph nodes, which is in agreement with other results[9] and with the concept of an inverse relation between a large tumor burden and efficacy of treatment. This response rate is consistent with previous reports,[10–12] as more than half of the patients (13 of 22) presented with a minimal metastatic disease localized to skin, subcutaneous tissue, and lymph nodes.

The toxicity observed was acceptable, and was comparable to that reported in other trials[7,10,13] and only once obliged us to interrupt treatment. Toxic effects either abated slowly or persisted with decreased severity throughout the treatment. The major symptom of toxicity was fatigue, which persisted as long as IFN was given, and was mostly responsible for restricting daily activities. An array of flu-like symptoms coincided with treatment initiation, but slowly abated as treatment was pursued. Neurologic toxicity reported by other authors[14] did not occur. Cutaneous toxicity noticed by others[15] was transient and did not require IFN to be stopped.

The therapeutic role of interferons in the treatment of HMMM and more generally of human cancer is not yet precisely established.[16] Further trials are necessary to confirm these first results and to determine the optimal dose and the optimal schedule of administration of IFN. Two schedules of administration have been proposed: high intermittent or low continuous dose; so far the series have been too limited to allow any conclusion. In both our experience and in others', responses were observed in

metastatic localizations of limited size, mostly confined to skin and lymph nodes.

In this trial, the response rate was moderate and the duration of response was short. However, it should be noted that three of our six responders had received prior chemotherapy for metastatic disease without any positive result, and that conventional systemic treatment usually does not provide consistent benefit in patients who have been previously treated with cytotoxic agents.

Considering both the IFN properties of immunomodulation and induction of cell differentiation and the IFN Phase II study results in the treatment of HMMM, this drug might be of interest in treating limited metastatic disease and as adjuvant therapy after complete surgical tumor removal. However, no clinical trial has so far been reported that supports this latter hypothesis. Furthermore, the use of combination therapy in future clinical trials appears justified by previous reports of interaction between IFN and another immunomodulatory agent[9] and of *in vitro* experiments showing evidence of possible interaction between human IFN and classic anticancer drugs.[17,18]

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