

Treatment of Multiple Myeloma With Recombinant α -Interferon

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Thirty-two patients with multiple myeloma were treated with recombinant α -interferon clone A (rIFN α A) daily by intramuscular injection with an initial dose of 12×10^6 U/m². Of 27 patients evaluable for response, tumor responses were obtained in seven of 14 previously untreated patients (50%) and two of 13 who had relapsed or failed prior chemotherapy (15%). In all patients who had tumor response, there was restoration from subnormal levels of serum immunoglobulins, an effect infrequently observed with chemotherapy. The median duration of

tumor responses exceeded 14 months (range, 6 to 20). Moderate-to-severe fatigue was the predominant side effect and necessitated dose reductions in all patients. We conclude that treatment of early stages of multiple myeloma with rIFN α A is beneficial because of the substantial response rate and the improvement in the synthesis of serum immunoglobulins. rIFN α A has a potential role in combination with other agents in the treatment of multiple myeloma.

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EARLY CLINICAL STUDIES of partially purified α -interferon (IFN α) reported antitumor activity in patients with multiple myeloma.^{1,2} Subsequent studies have confirmed the activity of both partially purified and cloned IFN α in a limited number of patients.³⁻⁶ In this study we have examined the activity of high doses of recombinant DNA-derived α -interferon (rIFN α A) in patients with multiple myeloma, including both previously untreated patients and those whose disease was refractory to prior chemotherapy.

A high response rate was found among previously untreated patients but limited activity in patients with refractory myeloma. In addition, we present evidence that rIFN α A restored subnormal levels of serum immunoglobulins to normal levels in all responsive patients, an effect not frequently observed in patients responding to chemotherapy.

MATERIALS AND METHODS

Patient population and study design. Thirty-two patients were entered in the study. Criteria for a diagnosis of multiple myeloma included a monoclonal immunoglobulin in serum or monoclonal light chains in urine (or both) and at least one of the following: atypical bone marrow plasmacytosis of 15% or more, osteolytic lesions on x-ray examinations related only to the increased plasma cells, or bone biopsy results revealing plasma cell proliferation. Eligibility criteria included a performance status of ≥ 60 (Karnofsky scale), an expected survival of ≥ 12 weeks, preserved renal (creatinine level of ≤ 2.0 mg/mL) and liver function, granulocyte count above 1,500/ μ L, and a platelet count above 100,000/ μ L. In all previously treated patients, we required that there were at least 4 weeks between the last treatment and the onset of interferon therapy.

All patients had a clinical examination and staging of their disease before initiation of rIFN α A treatment. Tests performed within 1 week of the first injection included complete blood cell counts, differential count, platelet and reticulocyte counts, 12-channel blood chemistry, coagulation parameters, urinalysis, electrocardiogram, chest x-ray, serum and urine protein electrophoresis, bone marrow examinations, and bone surveys. Serum immunoglobulins were determined by quantitative nephelometry and Bence Jones protein by immunoelectrophoresis. Tumor mass was assessed according to conventional criteria.^{7,8} All patients were observed by physical examination every 4 to 8 weeks. Peripheral blood cell counts were repeated once or twice each week and blood chemistry, urinalysis, reticulocyte count, and coagulation profile were repeated once a week. Serum and urine electrophoresis were performed every 2 to 4 weeks and bone marrow and bone surveys every 2 to 4 months.

The rIFN α A (Roferon) was provided by Hoffmann LaRoche, Inc (Nutley, NJ). The purified protein was made homogeneous by

sodium dodecyl sulfate-polyacrylamide gel electrophoresis, with a specific activity of 2 to 4×10^8 U/mg of protein. All patients signed an informed consent to participate in the study according to institutional policies. All patients received an initial dose of 12×10^6 U/m² by intramuscular injection. Treatment was given daily and continued for a minimum of 12 weeks. A 50% reduction in dose was allowed in the event of evidence of excessive toxicity. Patients who responded continued to receive daily treatment until either tumor progression or the completion of 12 months of treatment.

Criteria of response. Tumor response was defined as a $\geq 50\%$ reduction of serum myeloma protein and disappearance of Bence Jones proteinuria. Response in one patient with nonsecretory multiple myeloma was confirmed when previously marked plasma cell infiltrates disappeared on multiple bone marrow specimens. Serum immunoglobulin response was defined as an increase in IgM of ≥ 40 mg/100 mL to the normal value (≥ 50 mg/100 mL), an increase in IgA of ≥ 60 mg/100 mL to the normal value (≥ 90 mg/100 mL), and an increase in IgG of ≥ 400 mg/100 mL to the normal value (≥ 650 mg/100 mL).

RESULTS

Table 1 summarizes the characteristics of the study population, which included 26 patients at the University of Texas M.D. Anderson Hospital and six at Wisconsin Clinical Cancer Center. The extent of tumor mass was low or intermediate in all but four of the previously treated patients. Of the 15 previously untreated patients, eight were asymptomatic, and seven had symptoms referable to lytic lesions.

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Supported by a grant from Hoffmann LaRoche, Inc. Research conducted in part by the Clayton Foundation for Research and the James E. Lyon Medical Research Foundation.

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Submitted May 22, 1985; accepted July 27, 1985.

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0006-4971/86/6702-0004\$03.00/0

Table 1. Patient Characteristics

	Untreated	Prior Chemotherapy
No. of patients	15	17
Median age	57	58
Male/female	11/4	9/8
Protein type		
IgG	10	11
IgA	2	5
Others	3	1
Tumor mass		
High	0	4
Intermediate	5	5
Low	10	8

None of these 15 had hypoalbuminemia, hypercalcemia, or azotemia, but three had a hemoglobin value of <10 g/dL. Thus, most met the criteria for indolent myeloma.⁸ All previously treated patients had received combination chemotherapy with intermittent courses of melphalan and prednisone or combinations of alkylating agents and doxorubicin. Four patients were treated upon relapse from prior successful therapy. The remaining patients had disease refractory to preceding combinations of chemotherapy.

Tumor responses. Twenty-seven patients were evaluable for tumor response. Five were not evaluable because they received treatment for less than 2 weeks because of evidence of excessive toxicity. Table 2 shows the results of treatment. Tumor responses were obtained in seven of 14 previously untreated patients (50%), whereas only two of 13 patients responded after failing prior chemotherapy (15%). Among the nine who had responses, seven had a low-tumor mass, and two had an intermediate-tumor mass; five had IgG myeloma protein, three had IgA myeloma protein, and one had a nonsecretory myeloma. Tumor responses occurred within 1 to 4 months (median, 2 months) and lasted from 6 to 20+ months (median, 14+ months). Three previously untreated patients maintained tumor remission beyond 12 months without further interferon therapy. Five of seven previously untreated patients who did not respond to rIFN α A achieved tumor responses with subsequent chemotherapy.

Immunoglobulin response. Restoration of depressed levels of one or two of the normal serum immunoglobulins was observed in all patients who had tumor responses (Fig 1). The time needed to achieve normal immunoglobulin levels in these patients ranged from 3 to 10 months (median, 4.5 months). Restoration was observed in six of six patients with subnormal IgA levels, in seven of nine with subnormal

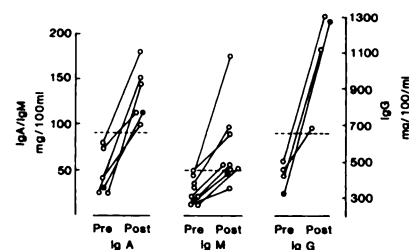


Fig 1. Nonparaprotein serum immunoglobulins in patients with tumor response. Data show pretreatment values and maximum posttreatment serum levels for nine patients with tumor response. Open circles indicate previously untreated patients and closed circles those who had received prior chemotherapy.

IgM, and in four of four with subnormal IgG. Figure 2 depicts the pattern of immunoglobulin response in one patient. Concurrent with the reduction of the myeloma protein in this patient, recovery of serum IgA and IgM was first observed after 3 months, with normal levels achieved after 6 months of treatment. In contrast, none of the patients who did not have a tumor response showed a detectable increase in serum immunoglobulins.

Toxicity. All patients were evaluable for toxicity, which was similar to that described in cancer patients receiving daily administration of rIFN α A.⁵ Fatigue and asthenia were the most common symptoms and accounted for most treatment interruptions, dose reductions, or drug discontinuations. A 50% dose reduction was indicated within 8 weeks of initiation of treatment in 20 patients (62%) and within 24 weeks in the remaining 12.

Hematologic toxicity included decrements of hemoglobin of 1 to 3 g/dL (median, 1.8 g/dL) within 4 to 12 weeks of treatment in 23 patients (72%). Transient severe granulocytopenia ($\leq 1,500$ cells per μ L) occurred in five patients (16%). A mild and slow decrease in platelet counts (between 50 and 100,000/ μ L) was observed in eight patients (25%), in keeping with prior observations.⁵ However, rapid onset of thrombocytopenia (within 2 weeks counts below 50,000 cells per μ L) consistent with an autoimmune phenomenon but reversible with discontinuation of rIFN α A developed in four other patients.⁹ These four patients, as well as one other with high-tumor mass who developed acute tubular necrosis after three doses of rIFN α A, received treatment for less than 2 weeks and were considered to be inevaluable for tumor response. Lastly, mild elevations of serum glutamic oxalo-

Table 2. Tumor Responses of Multiple Myeloma in Recombinant Interferon

Results of Treatment	No. Patients (%)	
	Untreated	Prior Chemotherapy
Tumor response	7 (50)	2 (15)
No change	5 (36)	7 (54)
Progressive disease	2 (14)	4 (31)
Total evaluable patients	14 (100)	13 (100)

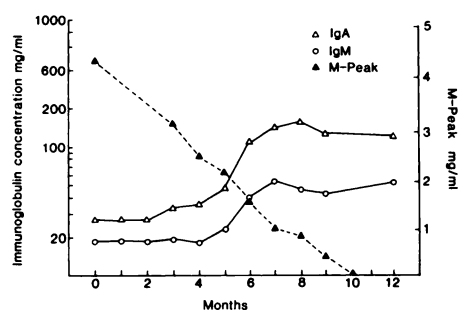


Fig 2. Pattern of recovery of nonparaprotein serum immunoglobulins in a patient with tumor response.

acetic transaminase (42 to 103 U/mL) were found in 16 patients (50%).

DISCUSSION

This study confirmed the therapeutic activity of rIFN α A in patients with multiple myeloma; such activity has been previously noted with partially purified IFN α interferon. We used a highly purified, single-molecular species of IFN α , which has also been effective in inducing remission of other B cell malignancies, including low-grade lymphomas and hairy cell leukemia.¹⁰⁻¹³ The 50% response rate among our untreated patients is superior to the 14% response rate recently reported in a study that used partially purified IFN α at lower doses (3×10^6 U/d).⁴

The greater activity in our study may be related to the type of interferon, the higher dose, or our selection of patients with early disease. A dose response effect to rIFN α A has been suggested in patients with Kaposi's sarcoma or renal cell carcinoma.^{14,15} However, that the present response rate in refractory myeloma is not better than that of other studies and that a higher response rate can be obtained in low-tumor mass myeloma with chemotherapy¹⁶ suggests that patient selection played a predominant role in our results.

Noteworthy is the disparity in the responsiveness among several B cell lymphoid malignancies to IFN α , from the relative resistance of intermediate- and high-grade lymphomas or advanced chronic lymphocytic leukemia,^{1,17} to moderate sensitivity of low-grade lymphomas and multiple myeloma,⁴⁻⁶ and to high susceptibility in hairy cell leukemia.¹² There is at present no information that may relate these different levels of sensitivity with the stage of differentiation or the expression of cellular receptors in the malignant cells. Of interest, however, is the recent finding of plasma cell-associated antigens on hairy cells¹⁸ that provides a phenotypic link between these two IFN α -sensitive tumors.

The recovery of normal levels of serum immunoglobulins in all patients with tumor response contrasts with a similar recovery in only 25% of comparable patients responding to chemotherapy.¹⁹ The deficiency in immunoglobulin synthesis in patients with multiple myeloma has been attributed to macrophage-derived suppressive factors.^{20,21} In a murine plasmacytoma model, the inordinate activity of macrophages was induced by a plasma cell-derived activating factor.²² Consequently, the restoration of normal levels of immunoglobulins in patients with tumor response may be explained by the reduction in tumor mass. However, in contrast to results with chemotherapy, the consistency of the effect in the responsive patients suggests that IFN α A elicited, in addition, favorable cellular interactions between regulatory and immunoglobulin-producing cells. In this regard, both IFN α and highly purified rIFN α A stimulate immunoglobulin production in vitro.^{23,24} Such stimulation was dependent on the presence of T helper cells and seemed to be related to the ability of IFN α to enhance the response of B cells to T helper-derived soluble factors.²³

We conclude that further studies of rIFN α A in patients with early stages of multiple myeloma are justified because of an adequate response rate associated with restoration of synthesis of serum immunoglobulins; further, rIFN α A does not preclude a later tumor response to chemotherapy. In fact, the tolerance to subsequent chemotherapy may be improved by reduction of the risk of infections in patients with a restored humoral immune response. The rIFN α A had acceptable toxicity at an average daily dose of 6×10^6 U/m². It is unknown whether lower and perhaps less toxic doses might achieve comparable results.

The low response rate in patients previously treated with chemotherapy was similar to our previous observations on rIFN α A in refractory multiple myeloma.⁵ However, our findings offer promise for further developments with rIFN α A as part of combination therapies. In this regard, in vitro synergism of IFN α with either γ -interferon, difluoromethylornithine, double-stranded RNA, or some chemotherapeutic agents has already been demonstrated.²⁵⁻²⁹ Further, in view of the antitumor activity of high doses of glucocorticoids in refractory myeloma,³⁰ clinical studies combining steroids and rIFN α A are of interest, both because of potential enhancement of the therapeutic activity of either agent and because of possible improvement in the tolerance to high doses of rIFN α A.

ACKNOWLEDGMENT

The authors wish to acknowledge the assistance of the nursing staff: Andrea Linder, Donnah Jones, Paula DeAvies, Margaret Harle, Sue Schmidt (M.D. Anderson Hospital and Tumor Institute), and Jill Aughey (Wisconsin Clinical Cancer Center). They also express their gratitude to John Kolsbun, a physician assistant; data managers Marion Stringer, Elaine Stehr, Sandra Ictech, and Brigetta Burgess; and to Linda Reckeweg for her impeccable secretarial assistance.

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