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Priming Therapy with Alpha-Interferon in Chemotherapy-Resistant Multiple Myeloma

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Nine patients with multiple myeloma were treated with alpha-interferon (IFN) priming followed by the previous chemotherapy regimen to which the patients had been resistant. Natural human leukocyte IFN (8 patients) or recombinant human IFN-2b (1 patient) at a dose of 5–6 × 10^6 IU s.c. was given for 1–2 weeks before chemotherapy, after which IFN was used either cyclically or continuously (3–6 × 10^6 IU every other day). Four patients responded; three had a good response based on reduction of the paraprotein level, and one patient had no further progress of his bone lesions. Two of the patients have had a prolonged response lasting 21 and 13+ months, respectively. IFN increased chemotherapy-related myelotoxicity considerably, and three patients died of granulocytopenic sepsis. The use of IFN priming may possibly offer an alternative for the treatment of some patients with resistant multiple myeloma.

KEY WORDS: Multiple myeloma interferons drug resistance.

INTRODUCTION

Alpha–interferon (IFN) is effective in the treatment of multiple myeloma. It increases the response rate when combined with primary chemotherapy[1] and may prolong the response duration and survival when used as maintenance therapy[2]. IFN alone has resulted in favourable responses in 15–30% of patients with resistant myeloma[3] and administration of IFN before reinstitution of chemotherapy (IFN priming), may enhance the effect of cytostatic agents in patients with relapsing or resistant myeloma[4,5]. The purpose of the present study was to clarify if IFN priming could reduce the resistance to second or third line chemotherapy in multiple myeloma. Despite the fact that this is only a small series our results suggest that IFN priming may have a role in the therapy of advanced multiple myeloma.

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PATIENTS AND METHODS

Data on the patients are presented in Table 1. All the patients (N = 9) were resistant to second (N = 3) or third line (N = 6) chemotherapy. The mean time interval from the beginning of the first chemotherapy regimen to IFN priming was 45 months (range: 10 to 101 months). The primed chemotherapies consisted of MOCCA (N = 4), VAD (N = 2), VCAP (N = 1), MP (N = 1) and CP (N = 1); see Table 1. The respective therapies were first used without IFN, and after demonstration of chemotherapy resistance (Tables 1 and 2) the same therapies were continued without delay (except in pat 9) with IFN priming.

Eight patients received natural human leukocyte IFN (Finnferon-Alpha^R, Finnish Red Cross Blood Transfusion Service, Helsinki, Finland) and one patient, recombinant human IFN-2b (Introna^R, Schering, New Jersey, USA). IFN, at a daily dose of 5 to 6 × 10^6 IU s.c., was started 1 to 2 weeks before reinstituting the initial chemotherapy, to which the patient had been unresponsive. Four patients used IFN cyclically, *i.e.*, after administration of the cytostatic regimen IFN was stopped and restarted

Table 1 Patient data

Pat	*Sex*	*Age*	*Myeloma*		*Previous treatments and responses (+ or −)**		*Time from 1st treatment to IFN (months)*
			-type	*-stage*			
1	M	52	IgG-L	III A	MP × 6	−	16
					MOCCA × 4	−	
					VAD × 3	−	
2	M	74	IgG-K	II A	MOCCA × 6	−	56
					VAP × 7	−	
					CP × 37	+/−	
3	M	72	B-J	III A	MP × 21	+	33
					MP × 3	−	
					MOCCA × 5	−	
4	M	65	IgA-K	II A	MOCCA × 7	+	43
					MOCCA × 7	+	
					MOCCA × 5	−	
					VAD × 6	−	
					MP × 2	−	
5	M	50	IgG-K	II A	MOCCA × 10	−	37
					VAP × 12	−	
					MP × 7	−	
6	F	67	IgG-K	II A	MP × 12	+/−	74
					MOCCA × 5	+/−	
					VCAP × 5	+	
					VCAP × 6	−	
7	M	68	IgG-L	II A	MP × 7	−	101
					MOCCA × 17	+	
					MOCCA × 7	+/−	
8	F	50	IgA-L	III A	MP × 4	−	10
					MOCCA × 3	−	
					VAD × 2	−	
9	F	58	B-J	II B	MP × 6	−	39
					MOCCA × 1	−	

* MOCCA: methylprednisolone 1 mg/kg p.o. D 1–7; vincristine 0.03 mg/kg, max 2 mg i.v. D 1; cyclophosphamide 10 mg/kg i.v. D 1; CCNU 40 mg p.o. D 1; melphalan 0.25 mg/kg p.o. D 1–4; VAD: vincristine 0.4 mg 8-hr inf. D 1–4; doxorubicine 9 mg/m² 1-hr inf. D 1–4; dexamethasone 40 mg p.o. D 1–4, 9–12, 17–20; VCAP: vincristine 1 mg i.v. D 1; cyclophosphamide 100 mg/m² p.o. D 1–4; doxorubicine 25 mg/m² i.v. D 1; prednisone 60 mg/m² p.o. D 1–4; MP: melphalan 9 mg/m² p.o. D 1–4; prednisone 1 mg/kg p.o. D 1–4; CP: cyclophosphamide 5 mg/kg p.o. D 1–4; prednisone 1 mg/kg p.o. D 1–4.

Table 2 Effect of IFN priming therapy in the responding patients

Pat	*Treatment —preceding therapy without IFN —IFN primed therapy*	*Paraprotein response (S.Ig:g/l, dU-prot:g)*	*Bone marrow (% plasma cells)*	*Bone lesions*	*Outcome*
1	VAD(× 3)	S-IgG:41.6; dU-prot:12.8	90	solitary	IFN for 7 mo, progressive disease, exitus in neutropenic sepsis
	IFN + VAD(× 7)	S-IgG:20.7; dU-prot: 0	90	solitary	
3	MOCCA(× 5)	dU-prot:4.6	30	numerous, in progress	remission with IFN priming
	IFN + MOCCA(× 10)	dU-prot: <0.1	<5	no progress	
4	MOCCA(× 5), VAD(× 6), MP(× 2)	S-IgA:10.3 – 24.6	80	numerous, in progress	IFN for 4 mo, progressive disease ad exitus
	IFN + MOCCA(× 3)	S-IgA:5.7	80	progression	
5	MP(× 7)	S-IgG:16.8	10	numerous, in progress	cessation of progression in bone lesions
	IFN + MP(× 10)	S-IgG:12.7	<5	no progress	

again, 1 to 2 weeks before the next cycle. Five patients were given IFN continuously at a lower dose (3 to 6×10^6 IU) every other day. Serum concentration and urine excretion of paraprotein, bone marrow aspiration and skeletal x-rays were performed to assess the effect of the priming therapy. Blood counts and hepatic and renal function tests were regularly followed. A good response was defined as a decrement of 50% or more of the serum paraprotein or 90% or more of the urine paraprotein excretion. The patient was also regarded as responsive to priming therapy if there was a cessation of progression of osteolytic lesions associated with otherwise quiescent disease.

RESULTS

Four of the nine patients responded to IFN priming therapy (Table 2). Three patients had a good response: serum paraprotein level decreased by 50 and 77% (patients 1 and 4) or daily proteinuria disappeared totally (pat 3). The disease stabilized in one patient (pat 5) who had biochemically quiescent myeloma but whose bone lesions had progressed during the preceding two years in spite of MOCCA, VAP and MP therapies. With IFN priming therapy there was a cessation in progression of the osteolytic lesions.

Patient 1

The effect of IFN priming was most evident in patient 1. He was primarily refractory to all treatments (MP, MOCCA, VAD). During VAD therapy alone serum IgG paraprotein was repeatedly at least 40 g/l and proteinuria 10–15 g/day. After the first IFN primed VAD cycle, urine paraprotein became undetectable, and serum paraprotein decreased by 50%. However, the bone marrow infiltration by myeloma cells remained unchanged at 90% and later on the disease also progressed as assessed by the biochemical profile. The patient died of sepsis during cytopenia after the 7th primed VAD cycle, 7 months after the initiation of the priming courses.

Patient 3

In patient 3 the remarkable response of urine paraprotein excretion to treatment, was associated with a normalization of the percentage of bone marrow plasma cell infiltration, i.e. he achieved remission which was maintained for 3+ months.

Patient 4

Patient 4 received recombinant IFN 5×10^6 IU daily combined first with pulses of high-dose corticosteroid. During this treatment the serum IgA level decreased from 24 to 15 g/l. A further decrease to 5.7 g/l was achieved by IFN priming and reinstitution of the MOCCA regimen. However, plasma cell infiltration of the bone marrow which was massive, did not improve, and the patient died of progressive disease after 5 months IFN primed chemotherapy.

Table 3 Bone marrow toxicity of IFN priming therapy

Pat	*Treatment —previous −primed*	*WBC nadir* ($\times 10^9$/l)	*Plt nadir* ($\times 10^9$/l)	*Complications*
1	VAD	0.6	11	sepsis in 2 of 3 cycles
	IFN + VAD	0.4	13	sepsis in 3 of 7 cycles; septic death
2	CP	N	N	—
	IFN + CP	1.4	N	
3	MOCCA	1.7	132	—
	IFN + MOCCA	1.4	41	
4	MOCCA	2.7	67	
	IFN + MOCCA	1.0	21	—
5	MP−/+IFN	N	N	—
6	VCAP−/+IFN	N	N	—
7	MOCCA	1.7	110	—
	IFN + MOCCA	0.1	41	septic death
8	VAD	2.1	92	—
	IFN + VAD	1.2	21	septic death

N = normal.
Patient no. 9 did not get any IFN primed chemotherapy due to rapid liver toxicity of IFN.
Plt = platelet.
WBC = leukocytes.

Patient 2
Patient 2 had a transient 21% decrease in the serum paraprotein level (S-IgG from 49.5 to 39.3 g/l) after starting the IFN primed CP therapy. However, this minor response soon disappeared and serum paraprotein levelled off at the same level it had been earlier for 1.5 years; IFN was stopped after 8 months.

Patients 6, 7, 8, 9
Patient 6 did not respond to IFN primed VCAP, and after 4 months IFN was stopped. Patients 7 and 8 died of granulocytopenic sepsis soon after the first IFN primed chemotherapy cycles (MOCCA and VAD) were given. In patient 9 IFN therapy was associated with increasing levels of liver transaminases, and therapy was stopped. Thus, in patients 7, 8 and 9 the treatment responses could not be evaluated appropriately.

The observed responses to IFN priming were evident soon after the first primed chemotherapy cycle. In patients 1, 2 and 4 the duration of response was short, and the disease progressed after one or two IFN primed cycles of chemotherapy. Patients 3 and 5 have retained their response for 13+ and 21 months, on continuous IFN. The mean duration of IFN primed treatment in all patients was 5.3 months (range: 12 days–14+ months).

IFN accentuated chemotherapy-related bone marrow toxicity and other side-effects The leukocyte and platelet nadirs after the previous chemotherapy cycles and the respective IFN primed cycles are shown in Table 3. More pronounced cytopenias were recorded in all except 2 patients after IFN priming, compared to the same chemotherapy given without IFN. In fact, the three patients with the lowest leukocyte nadirs after IFN primed cytostatics died of sepsis, two of them after their first IFN primed chemotherapy cycle. The cytopenic effect of IFN priming treatments was more marked on leukocytes than platelets.

Most patients had transient fever and flue-like symptoms at the beginning of IFN therapy. The IFN dose of patient 5 was reduced from 6×10^6 IU daily to 6×10^6 IU every other day because of chronic fatigue. The IFN therapy had to be stopped because of marked side-effects in two patients. Patient 2 became extremely fatigued, however this symptom disappeared after discontinuation of IFN, which had been given for 8 months. Patient 9 had marked increase in the levels of liver transaminases, with doses of both 6 and 3×10^6 IU given daily for 11 and 5 days, respectively, and IFN had to be discontinued.

DISCUSSION

The response rate, obtained by IFN priming therapy in patients with resistant myeloma, which includes three patients with good biochemical responses and one patient with stabilized bone disease, is encouraging. It supports the suggestion made by Costanzi and Pollard[4], that IFN therapy may be beneficial before reinstituting chemotherapy in patients with relapsing myeloma. However, they used IFN priming in relapsing patients without using the same previously effective chemotherapy alone. Thus, the possibility of the responses being due to chemotherapy alone in their series cannot be excluded (6 responders out of 9 relapsing patients). Two of the 9 patients with refractory myeloma in that series had a minor response when treated with IFN primed chemotherapy. In our study we first excluded the possible effect of chemotherapy alone and responses could thus be attributed to IFN priming. Two patients (1 and 9) were primarily refractory, and one of them responded to IFN priming.

Responses with IFN alone may be achieved in 15–30% of therapy-resistant myeloma patients[3]. In our patients we could assess the effect of IFN without chemotherapy in only one (pat 4). Half of the final decrease in paraprotein level was observed after initial IFN and steroid therapy while the second part of the response occurred during the IFN primed chemotherapy.

Recent *in vitro* studies have shown that IFN may inhibit immunoglobulin synthesis or secretion by myeloma cells, and this effect may exceed the antiproliferative capacity[6,7]. In fact, a "paralysis" of paraprotein secretion may falsely mimic a true treatment response. In two patients (1 and 4) this kind of transient mimicry was evident, because the bone marrow examination and clinical disease evolution were not consistent with a true response. However, in one patient the decrease in paraprotein level was associated with diminished bone marrow plasma cell infiltration (pat 3) and in another with cessation of progression of osteolytic lesions (pat 5). These observations demonstrate that it is possible to control progression of disease using IFN primed chemotherapy in some patients with resistant myeloma. This concept is shared by other authors[4,5,8].

The mechanism by which IFN reverses the resistance against cytostatics is incompletely under-

stood. In one myeloma patient VAD resistance was reversed with verapamil, a possible inhibitor of p-glycoprotein[9]. Multi-drug resistance associated with overexpression of p-glycoprotein has been found in some haematological malignancies[10,11] and in resistant myeloma, IFN may act by modulating the expression of the multi-drug resistance gene.

It should be noted that IFN priming therapy was associated with considerable toxicity. The most severe side-effect was the increase in chemotherapy-induced myelosuppression, especially leukopenia. Myeloma patients with longstanding disease who have received many chemotherapy cycles, are especially prone to myelosuppression. Caution is consequently needed when IFN and cytostatics are combined. Three patients in our study, all with rapidly progressive, aggressive disease, died of sepsis with severe granulocytopenia. The two patients who died after the first primed chemotherapy cycle had received IFN for 11 and 12 days before MOCCA and VAD treatments, respectively. The third patient was initially cytopenic due to heavy bone marrow infiltration and died after the 7th primed VAD cycle. Thus, in patients with heavy bone marrow plasma cell infiltration, IFN should be administered cautiously in order to avoid severe neutropenia.

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