Eur J Cancer Clin Oncol, Vol. 22, No. 9, pp. 1111–1116, 1986.
Printed in Great Britain

0277-5379/86$3.00+0.00
Pergamon Journals Ltd.

Recombinant Interferon Alfa-2C versus Polychemotherapy (VMCP) for Treatment of Multiple Myeloma: a Prospective Randomized Trial

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Abstract—*Forty-two previously untreated patients with multiple myeloma were entered in a prospective, randomised trial comparing recombinant interferon alfa-2C monotherapy with VMCP (vincristin, melphalan, cyclophosphamide and prednisolone). Both treatment arms were comparable for the stratification variables such as paraprotein type, stage of disease, and renal function. Rec. interferon effected* 14% *responses and* 29% *minor responses, while* 57 *and* 32% *of VMCP-treated patients achieved a pathologically documented remission* ($P < 0.001$). *The time on initial treatment was significantly shorter in the IFN group* (3.2 months) *than in the VMCP group* (7.6 months). *In four patients in the IFN arm, primary treatment had to be changed according to progressive or severe stationary disease. Since all four patients responded to second line therapy (VMCP) no significant difference has been observed between the two groups in survival (median follow-up* > 12 months).

Despite this clear superiority of the conventional four-drug polychemotherapy, there was some suggestion that IFN might be particularly active in cases with low tumor-burden (stage I, II), *and light-chain or IgA paraprotein type.*

INTRODUCTION

EXPERIMENTAL evidence of significant antiproliferative activity of human leukocyte interferon on a human myeloma cell line [1] prompted its use in patients with multiple myeloma. The first clinical report in 1979 [2] on partial and complete responses in four chemotherapy-resistant patients treated with interferon were promising enough to arouse the special interest of the scientific community and stimulate hopes in the public. *In vitro* studies by our group also revealed a significant inhibitory activity of lymphoblast interferon on myeloma stem cell growth [3]. However, the subsequent employment of the limited amounts of natural human leukocyte interferon in a systematic phase II study on small numbers of both previously untreated and pretreated myeloma patients failed to match the initial high response rates [4]. The same interferon preparation was also applied in a randomized clinical trial comparing interferon and melphalan–prednisone [5]. The response rates achieved in patients with light chain and IgA myeloma on interferon treatment were similar to those observed in patients under chemotherapy, but cases of IgG myeloma had significantly fewer responses to the interferon treatment [5].

The introduction of recombinant DNA technology provided the means for large-scale supplies of homogenous, highly purified alfa-interferons and rendered more comprehensive clinical studies possible. The European Myeloma Study Group for Interferon organized a prospective randomized trial comparing the effect of recombinant-interferon alfa-2C monotherapy and VMCP-polychemotherapy. The results of that study in pre-

Accepted 12 March 1986.
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viously untreated patients with multiple myeloma are documented in this report.

MATERIALS AND METHODS

Patients

Owing to the collaboration of nine institutions, a total of 42 patients with the confirmed diagnosis of multiple myeloma were entered into this study between August 1983 and November 1984. Entry was restricted to previously untreated patients with measurable disease parameters (monoclonal protein), manifestations of progressive disease requiring cytostatic tratment, and serum creatinine levels < 20 g/l. Patients with smoldering, non-progressive stage I or non-secretory myeloma, patients with plasmocytoma or plasma cell leukemia, cases with renal insufficiency (creatinine > 20 g/l), and pretreated patients were not acceptable for study. Patients characteristics are summarized in Table 1. Nine patients were excluded from the final evaluation; one patient refused treatment, two died within 2 weeks after start of therapy, and two had significant protocol violations. While 18 patients in the interferon group and 19 in the chemotherapy arm were eligible for evaluation of toxicity, there were four additional cases with rapidly progressing disease in the IFN arm, who did not achieve the minimum of 6 weeks' treatment required for eligibility of efficiency evaluation. Thus, the therapeutic effect could be evaluated in 14 patients of interferon treatment and in 19 patients on chemotherapy.

Treatment

Recombinant interferon alfa-2C (produced by Boehringer Ingelheim International) was provided lyophilized and highly purified (specific activity 3.2×10^8 IU/mg) for intramuscular application according to the following regimen: 10×10^6 U/d day 1–3; 20×10^6 U/d day 4–13; 10×10^6 U/d 5 × week day 14–90 and 10×10^6 U/d 3 × week following day 91.

In the chemotherapy arm VMCP (vincristine 1.4 mg/m^2, melphalan 15 mg/m^2, cyclophosphamide 450 mg/m^2, and prednisolone 40 mg/m^2 day 1–7, 20 mg/m^2 day 8–14 orally) was administered. The courses were repeated at 4–6 week intervals as determined by the degree of myelotoxicity. Patients were randomized to either treatment arm according to the following criteria: institution, paraprotein type, stage, and renal function (creatinine < 20 g/l). The minimal treatment duration required for eligibility of efficiency evaluation was 6 weeks for IFN and 12 weeks (three cycles of therapy) for VMCP. Patients who failed to respond during treatment with interferon were to be crossed over and treated with the alternative regimen. If tumor progression occurred on standard therapy, patients were to receive alternative polychemotherapy.

Table 1. Patient characteristics

		Number of patients
Entered		42
Eligible		33
Age		
Median	63 yr	
Range	30–88 yr	
Stage		
I		5
II		19
III		18
M-component		
IgA		13
IgG		24
K/l		29/12*
Serum creatinine		
1.5 mg/100 ml		40
1.5–2.0 mg/100 ml		2

*One patient not determined.

Response criteria

Response to therapy was defined mainly according to the criteria proposed by the Committee of the Chronic Leukemia Myeloma Task Force [6]. A maintained reduction of the serum monoclonal protein concentration or the urinary excretion of M-protein (if the initial value had exceeded 1.0 g/24 hr) to less than 50% of the initial amount was considered a "response". A "minor response" was defined by the maintained decrease in serum or urinary M-protein within the range of 25–50%. The criterion for progressive disease was fulfilled by the observation of one or more of the following changes:

(1) Increase of the serum M-component concentration to at least 125% of the pretreatment level,
(2) 100% increase of the urinary protein excretion (if the initial value had exceeded 1.0 g/24 hr)
(3) Serum calcium > 3 mmol/l or progression of osteolytic lesions.

A disease course which fulfilled neither the criteria for response, minor response nor progression was categorized as stable.

Toxicity

Hematological toxicity was classified according to the WHO-criteria: toxicity grades I and II signified moderate leukopenia (1500–3999/μl) and/or thrombopenia (5×10^4–1.5×10^5/μl); grades III and IV were defined by severe leukopenia (< 1500/μl) and/or thrombocytopenia (< 50.000/μl).

Statistical evaluation

Curves of the probability of survival were calculated from the date of beginning therapy by the method of Kaplan and Meier [7]. Statistical significance for survival curves was determined by the Wilcoxon (Breslow) test.

RESULTS

Four of the patients on IFN considered eligible for evaluation of side-effects were not evaluable for the therapeutic efficacy, since rapidly progressive disease within less than 6 weeks of interferon made a cross over to chemotherapy mandatory. In the remaining 14 patients, IFN induced tumor response in two (14%) and minor responses in four patients (29%). Seven patients remained stable and one showed slowly progressive disease.

Chemotherapy in 19 patients effected response in 11 (57%) and minor responses in six patients (32%). Two cases (11%) showed disease stabilisation (Table 2). The combined rate of responses and minor responses was with 43% in the interferon group significantly lower than the 89% in the standard chemotherapy arm ($P < 0.001$).

The proportion of patients responding to interferon declined gradually from patients with disease stage I–III (Table 3a). With respect to paraprotein type, in the interferon group the response rate was higher in IgA myeloma than in the IgG allotype. All three patients with IgA M-component responded, while the response rate for IgG myeloma was only 3/10 (Table 3b). The high frequency of remissions in the VMCP arm did not allow similar comparisons for that group. The median time from the beginning of treatment to the unequivocal manifestation of response was 10 weeks (range 4–26 weeks) in the chemotherapy group. In the two patients responding under interferon treatment, results were first detected after 4 and 13 weeks, respectively. The median time until manifestation of minor response was 4.5 weeks in the standard group and 3.5 weeks in the IFN arm.

Follow up of the patients has been conducted for > 12 months. The median time of initial therapy for all patients in the IFN group was 3.2 months as opposed to 7.6 months in the chemotherapy arm. Since primary treatment had to be changed in four patients in the IFN group according to progressive or severe stationary disease not responsive to treatment, so far, no significant difference has been observed between the two groups in survival ($P = 0{,}95$, Fig. 1).

Toxicity

Dosage reduction, mainly owing to psychological, neurologic, or hematologic side-effects, became necessary in 4/18 patients on interferon. In the chemotherapy group the dosage had to be decreased because of myelosuppression in 4/19 patients.

The side effects observed in both treatment arms are listed in Table 4. Moderate hematological toxicity (grades I and II) was observed in 10 patients (56%) on IFN and in six cases (32%) on conventional cytostatic drugs. Severe hematological toxicity (grades III and IV) occured in more patients on standard treatment than in the interferon group. This trend ($P < 0.1$) was mirrored in the clinical consequence, as severe infections were three times more frequent in chemotherapy patients than in the interferon group. Pulmonary infarction occured in three cases on standard therapy but in none of the patients under interferon treatment. Fever unconnected with infection was more common in patients under IFN where it was observed in 68% during the initial treatment phase. However, under continuation of interferon treatment, the fever regressed completely. Influenza-like symptoms such as chills, fatigue, feebleness, myalgias, and arthralgias were frequently seen during treatment with interferon. Nausea, vomiting, and liver dysfunction usually regressed after dosis reduction. One patient showed an exacerbation of his preexisting Parkinson's disease with a stiffness endeavour. Two patients experienced severe confusion with loss of concentration and expressive dysphasia; one patient developed dysfunction of the autonomic nervous system with peripheral paresthesia, and in one case a preexisting depression was exacerbated. All of the described symptoms vanished after dosis reduction.

DISCUSSION

The observed proportion of 43% in which interferon showed at least some degree of anti-

Table 2. Response to recombinant interferon alfa-2C and VMCP in previously untreated patients with multiple myeloma

		Treatment results			
Treatment arm	Patients eligible	Response	Minor	Stable	Progression
IFN alfa-2C	14	2 (14%)	4 (28%)	7 (50%)	1 (7%)
VMCP	19	11 (57%)	6 (32%)	2 (11%)	0 (0%)

Table 3a: Rate of clinical response in the interferon and chemotherapy arm in relation to paraprotein type*

M-Protein	rec. IFN alfa-2C	VMCP
IgG	3/10	9/9
IgA	3/3	6/8
Light chain	0/1	2/2

*Including minor response.

Table 3b: Rate of clinical response in the interferon and chemotherapy arm in relation to stage of disease (Durie und Salmon staging system)*

Stage	rec. IFN alfa-2C	VMCP
Stage I	2/3	0/0
Stage II	3/7	8/9
Stage III	1/4	9/10

*Including minor response.

*Table 4. Total episodes of toxicity reported**

Side-effects	rec. IFN alfa-2C (n = 18)	Chemotherapy (n = 19)
Hematologic toxicity		
Grade I/II	10 (56%)	6 (32%)
Grade III/IV	3 (17%)	10 (53%)
Infection	2 (11%)	6 (32%)
Pulmonal infarction	–	3 (16%)
Fever	13 (68%)	1 (5%)
Fatigue	4 (22%)	–
Chills	3 (17%)	–
Nausea	3 (17%)	1 (5%)
Vomiting	3 (17%)	2 (11%)
Feebleness	3 (17%)	–
Liver dysfunction	3 (17%)	2 (11%)
Myalgia/arthralgia	2 (11%)	–
Confusion	2 (11%)	–
Depression	1 (6%)	–
Autonomic dysfunction	1 (6%)	–

*The mean duration of treatment was 3.2 months in the interferon group, and 7.6 months in the VMCP group.

proliferative activity in cases of multiple myeloma supports the hope that interferon might add to the therapeutic armament of active drugs for that disease. Still, there cannot be any doubt that as monotherapy it is significantly inferior to the four-drug polychemotherapic VMCP which effected 89% responses including minor responses. The observed frequency of clinical remissions achieved with rec. interferon alfa-2C, as well as the superiority of conventional chemotherapy for treatment of multiple myeloma is in accordance with most of the studies previously published [8, 5].

Our results also seem to confirm that—though superior in activity to beta interferon [9–11]—apparently there is no fundamental pharmacological difference in the activity of natural leukocyte interferon [4, 5, 12, 13] and alfa interferon produced by recombinant DNA technology [8].

Although our interferon data were derived from a relatively small number of patients, the declining rate of responses in patients with stage III myeloma when compared to those with stage I/II ($P < 0.05$) provokes speculations that interferon might be particularly active in cases with low

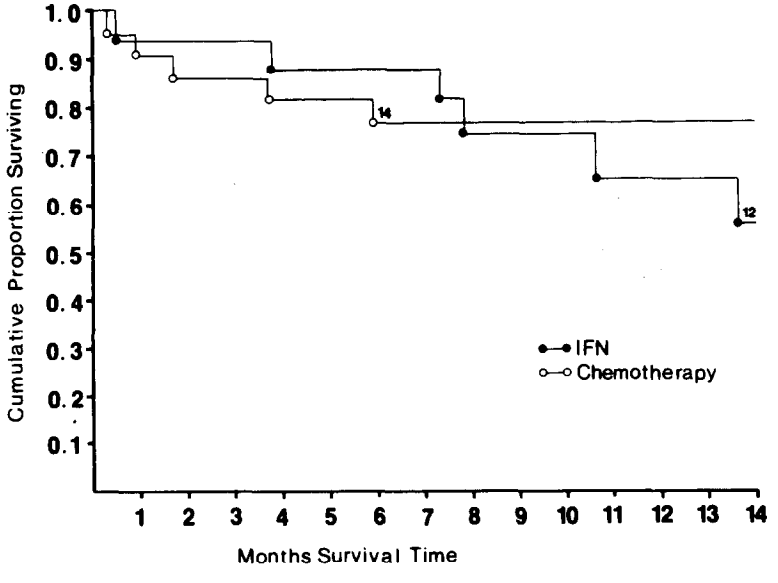

Fig. 1. Comparison of survival between the 14 (eligible) patients treated with recombinant interferon alfa-2C and the 19 patients treated with VMCP. Since four patients with clinical response to second-line therapy in the IFN treatment arm were included in this analysis, there was no statistical difference between the two groups in survival.

tumor mass. Another interesting finding represents the association between IgA myeloma and high response rates to interferon treatment. Similar observations, namely preferential interferon activity in IgA and light chain disease have been reported by the Swedish working group [5], where an ongoing trial is being restricted to patients with IgA and light chain myeloma. Interestingly, in the Anglo-American trial no allotype specifity was found [8].

Rather in contrast with the lower response rate achieved in the interferon group, there seems to be no significant difference in total survival of patients in either treatment arm (up to a follow-up of › 12 months). It must be emphasized, however, that in four patients IFN had to be withdrawn because of insufficient therapeutic results; all four patients responded to subsequent alternative chemotherapy with VMCP. While this fact certainly restricts the feasability of a direct comparison of survival data between the IFN and chemotherapy group in this study, it suggests that secondary treatment (VMCP) will yield good therapeutic results.

In summary, rec. IFN alfa-2C given as single treatment in patients with multiple myeloma is clearly inferior to conventional therapeutic approaches. However, there probably exist certain subgroups of patients (i.e. those with low tumor burden, and/or with IgA or light chain disease) that are likely to benefit from IFN treatment. Based on preliminary *in vitro* [14,15] and *in vivo* data [16–18] suggesting a potential synergism of interferons and cytotoxic drugs, it might be of particular interest to determine in these specific subgroups of patients with multiple myeloma, if such combined treatment modalities could further increase the therapeutic effectiveness of interferons.

Acknowledgements—Additional members of the EMSI trial group who contributed to this study: H. Abel (St. Josef Hospital, Wiesbaden, FRG), Z. Bernemans (Academic Hospital, Antwerp, Belgium), J. Bury (University Hospital Baviére, Liége, Belgium) and D. Gangji (Erasmus Hospital, Brussels, Belgium).

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