

RECOMBINANT INTERFERON ALFA-2C TREATMENT VERSUS  
POLYCHEMOTHERAPY IN MULTIPLE MYELOMA

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INTRODUCTION

Experimental evidence of significant in vitro antiproliferative activity of human leukocyte interferon (6) prompted its use in patients with multiple myeloma. The first clinical report in 1979 (11) 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. However, the subsequent phase II and phase III studies using the limited amounts of natural human leukocyte interferon in small numbers of both previously untreated and pretreated myeloma patients failed to match the initial high response rates (2,9). After the introduction of recombinant DNA technology ample amounts of homogeneous, highly purified alfa-interferon were available for more comprehensive clinical studies. The European Myeloma Study Group for Interferon organized a prospective randomized trial comparing the effect of recombinant-interferon alfa-2C monotherapy and VCMP-polychemotherapy. The results of that study in previously untreated patients with multiple myeloma are documented in this report.

MATERIALS AND METHODS

Patients:

42 patients with the confirmed diagnosis of multiple myeloma participated in this multi-center study. Entry was restricted to

- (2) 100% increase of urinary protein excretion (if the initial value had exceeded 1.0 g/24 hours),
- (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 ( $1,500-3,999/\mu\text{l}$ ) and/or thrombocytopenia ( $5 \times 10^4 - 1.5 \times 10^5/\mu\text{l}$ ); grades III and IV were defined by severe leukopenia ( $<1,500/\mu\text{l}$ ) and/or thrombocytopenia ( $<50,000/\mu\text{l}$ ).

#### RESULTS

Interferon treatment induced tumor responses in 2 (14%) and minor responses in 4 (29%) of the 14 eligible patients. 7 patients remained stable and 1 showed slowly progressive disease. Chemotherapy effected responses in 11 (57%) and minor responses in 6 (32%) of the 19 patients on standard treatment. 2 cases (11%) showed stable disease, none progressed within the observation period. The combined rate of responses and minor responses in the interferon group was with 43% significantly lower than the 89% observed in the standard chemotherapy arm ( $p < 0.001$ ).

TABLE 1. Comparison of Response Rates to Interferon Treatment

Treatment State	No. Treated	Response	Clinical Trial
untreated	14	2 (14%)	present study
untreated	74	9 (12%)	Ahre et al., 1984
refractory	19	2 (11%)	Constanzi et al., 1984
relapsing	19	5 (26%)	Constanzi et al., 1984

The proportion of patients responding to interferon declined gradually from patients with disease stage I to those with stage III. Response rates to interferon were higher in IgA myeloma (3/3) than in the IgG allotype (3/10). The high frequency of responses in the chemotherapy 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 VMCP group. In the two patients responding under interferon treatment, remissions were first noticed after 4 and 13 weeks. The median time until manifestation of minor response was 4.5 weeks in the standard group and 3.5 weeks in the interferon arm.

The following side effects were observed: Moderate hematological toxicity (grades I and II) occurred in 10 (56%) patients on interferon and in 6 (32%) cases on conventional cytostatic drugs. Severe hematological toxicity (grades III and IV) was manifested 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 occurred 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 interferon where it was observed in 68% during the initial treatment phase, but subsided with the continuation of interferon treatment. 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 paraesthesia, and in one patient a preexisting depression was exacerbated. All of the described symptoms vanished after dosis reduction. Dosage reductions due to the listed side effects became necessary in 13/18 patients on interferon. In the chemotherapy group the dosage had to be decreased because of myelosuppression in 4/19 patients.

## DISCUSSION

The observed proportions of 14% responses and 29% in which interferon showed some degree of antiproliferative activity in cases of multiple myeloma are in accordance with the recently reported results of other investigators (tab.1). In the Swedish trial comparing a Cantell preparation of natural leukocyte interferon with melphalan-prednisolone in untreated myeloma cases, the response rates were 14% for interferon and 43% for

melphalan-prednisolone (1). Alexanian et al. reported responses in 25% untreated and in 11% refractory or relapsing patients with the same interferon preparation (2). Application of recombinant interferon alfa-2 resulted in response rates of 11% in chemotherapy-refractory and 26% in relapsing patients (5). This indicates that - though definitely superior in activity to beta-interferon (3,12,7) - apparently there is no fundamental pharmacological difference in the activity of alfa-interferon produced by recombinant DNA technology (5) and natural leukocyte interferon (1,9,10,11).

Results obtained from patients with non-Hodgkin lymphomas indicate that interferon preferentially benefits patients with slowly proliferating lymphomas of low malignancy (8). The same might hold true for multiple myeloma. Interferon seems to be particularly active during the early stages of the disease. However, this assumption is based on a relatively small number of patients and needs to be confirmed by further studies.

Another interesting result is the statistically significant 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 (1) where an on-going interferon trial is being restricted to patients with IgA and light chain myeloma. In the Anglo-American trial, no allotype specificity could be found (5). Since our own sample is not large enough to allow definite conclusions, this matter should be considered in future investigations.

Judged by the response rates achieved in this trial, there can be little doubt that as a monotherapy interferon is significantly inferior to the four-drug polychemotherapy VMCP which in our patient group effected 89% responses and minor responses. Still, in accordance with other published investigations, our results support the hope that interferon might add to the armament of active drugs in treatment of multiple myeloma.

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 Bavière, Liège, Belgium), G. Fillet (University Hospital Bavière, Liège, Belgium), D. Cangji (Erasmus Hospital, Brussels, Belgium), and M. Peetermans (Academic Hospital, Antwerp, Belgium).