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Interferon Therapy During the Plateau Phase of Multiple Myeloma: An Update of the Swedish Study

Jan Westin, Agostino Cortelezzi, Martin Hjorth, Stig Rödjer, Ingemar Turesson and Göran Zador for a cooperative study group

A multicentre clinical trial was carried out in order to evaluate the effect of interferon (IFN) in patients with multiple myeloma. Patients (n = 120) who had shown response to conventional intermittent melphalan-prednisone induction therapy, and achieved a plateau phase, were randomized at that point to receive either interferon alfa-2b in a dose of 5 million units (MU) three times per week or no therapy. This report presents the results of an interim analysis, performed when the patients had been followed for a median of 20 months. The duration of the plateau phase was significantly longer in the IFN arm (59 weeks), compared to the no therapy arm (26 weeks). A total of 34 deaths have occurred, 13 in the IFN arm and 21 in the no therapy arm. In spite of the high median age of the patients studied (70 years), most patients were able to tolerate a full or only slightly reduced IFN dose.
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INTRODUCTION

FOR MORE THAN 10 years, it has been known that interferon (IFN) can be effective against multiple myeloma [1]. Several studies have demonstrated that both previously untreated patients, and patients with advanced disease may benefit from IFN therapy [2-4]. The given dose has varied considerably between the reported studies, and IFN has been given either alone or with melphalan-prednisone (MP) or with combination chemotherapy programmes [5]. In spite of these efforts, the precise role of IFN in the treatment of multiple myeloma is still not clearly defined. However, from the reported results it seems reasonable to suppose that IFN should have the best chance of exerting its effect in patients with early disease, and/or with a minor tumour burden.

Based on this background, in 1987 we initiated a multicentre clinical trial of interferon alfa-2b in patients with multiple myeloma who had achieved a response and stable disease (plateau phase). Our main hypothesis was that IFN therapy might prolong the duration of the plateau phase.

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PATIENTS AND METHODS

A total of 39 Swedish clinics and one Italian clinic participated in the trial. Six of the clinics belonged to university hospitals, while the rest were located in county hospitals. The general design of the study is shown in Figure 1.

The participating clinics were requested to report all newly diagnosed cases of multiple myeloma during the study period, as well as patients ineligible for melphalan and/or IFN therapy. In this way, a total of 432 myeloma patients were registered. Details of the patients who were not started on MP therapy and/or considered ineligible for randomization will be found in the final report.

Patients were included in the study during a 2-year period, from 1 September 1987 to 1 September 1989. A total of 120 patients were randomized in the clinical trial.

Criteria for inclusion and response

Only previously untreated patients with symptomatic multiple myeloma in stages II-III [6] were included in the

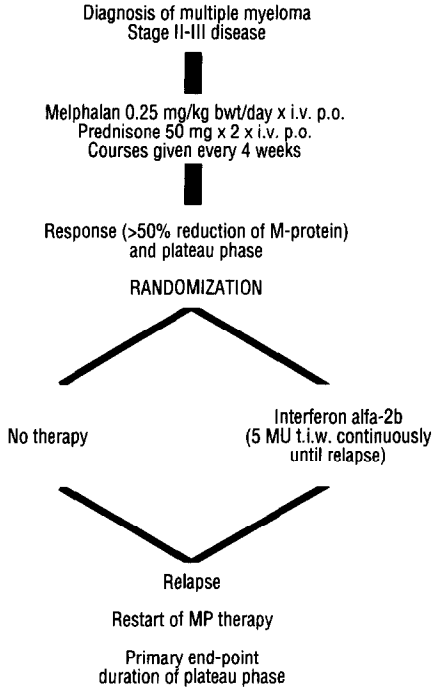

Fig. 1. Design of the study. The definitions of response, plateau phase and relapse are given in the text.

study. The diagnosis of myeloma was based on the following findings: (a) a serum M-component concentration above 30 g/L (IgG) or 20 g/L (IgA), or a urine light chain excretion >1 g/24 h; (b) plasma cells in bone marrow smears >10%; (c) osteolytic bone destruction. For an unequivocal diagnosis of multiple myeloma, a combination of a+b, or a+c, or b+c in the presence of a measurable M-component in a concentration lower than stated above, was needed.

Response. Response was defined as a reduction of the concentration of a serum M-component to <50% of the initial value, and of a urine M-component to <0.2 g/24 h. These findings should be accompanied by definite signs of clinical and laboratory improvement.

Plateau phase. A plateau phase was considered present when three consecutive measurements of the M-component concentration (ideally taken with an interval of 4 weeks) showed a variation not more than ± 10% (serum) or were <0.2 g/24 h (urine).

Relapse. Relapse was considered present when three consecutive M-component concentrations had shown an increase to >25% above the plateau phase level (serum), or to >1 g/24 h (urine).

End-point. The primary end-point of the study was the duration of the plateau phase, calculated from the time of randomization to the last of the M-component measurements needed to define relapse. In addition, patients were followed with regard to survival, compliance to the IFN therapy, and toxicity.

Dose intensity. Dose intensity was, in this report, calculated as the percentage of the scheduled IFN dose obtained during the available follow-up time. Dose intensity was graded as 90-100%, 60-90%, 20-60% and 0% (discontinued therapy).

Side effects. Side effects were graded 0-4 according to WHO. This report is mainly concerned with IFN effects on the peripheral blood cells, and the central nervous system side effects (chronic fatigue syndrome).

Final analysis

All results in this communication are preliminary, and mainly based on an interim analysis performed in October 1990. The final evaluation of the study will not be performed until after 1 June 1991.

RESULTS

A total of 120 patients were randomized, 59 to IFN therapy and 61 to no therapy during the plateau phase. Two patients, who initially had agreed to participate in the study and were randomized to receive IFN never started IFN therapy. For this report, however, both these patients were included in the IFN arm.

The treatment arms have been compared with regard to median age, proportion of patients older than 75 years, sex, stage, renal function, Ig class, haemoglobin, serum albumin and serum calcium (Table 1). No significant difference was observed between the two groups.

The treatment arms were also compared with regard to the number of MP courses given before randomization. The median in both arms was seven courses (Table 1). The median time used to define the plateau phase amounted in the IFN arm to 88 days, and in the no therapy arm to 98 days (Table 1).

Table 1. Randomized patients, clinical and laboratory findings at diagnosis

	Interferon (n = 59)	No therapy (n = 61)
Age (median ± S.D., years)	70 ± 8	70 ± 10
Patients > 75 years old	22	22
Male/female ratio	1.17	0.97
Type of myeloma		
IgG	35	33
IgA	14	22
light chain disease	10	6
Haemoglobin (mean ± S.D., g/l)	115 ± 15	114 ± 20
Serum albumin (mean ± S.D., g/l)	35 ± 6	34 ±7
Serum calcium (mean ± S.D., mmol/l)	2.65 ± 0.4	2.69 ± 0.4
Serum beta-2-microglobulin (mean ± S.D., mg/l)	4.4 ± 3.2 (n = 20)	3.9 ± 2.6 (n = 18)
Stage (Durie and Salmon, 1975)[6]		
I	1	0
II	23	19
III	35	42
II B + III B	9	9
Number of melphalan-prednisone courses given before randomization (median)	7	7
Time needed to define the plateau phase (mean ± S.D., days)	88 ± 28	98 ± 32

Present state of the study

An interim analysis was performed on 1 October 1990, when the median observation time of the randomized patients was 20

months. At that time, 24 of 59 patients in the IFN arm remained in plateau phase, but only nine patients in the no therapy arm. The number of relapses in the IFN arm was 33 (56%), and in the no therapy arm 52 (85%). Two patients in the IFN arm had died from intercurrent disorders while still in plateau phase (see below).

The median duration of the plateau phase was 59 weeks for the patients in the IFN arm and 26 weeks in the no therapy arm. The difference is highly significant ($P < 0.001$, log-rank test, two-tailed).

Up to the date of the interim analysis, a total of 34 patients had died, 13 in the IFN arm and 21 in the no therapy arm (Table 2). All 21 patients in the no therapy arm died from multiple myeloma ($n = 19$), or from some other cause but with the myeloma in an uncontrolled progressive state ($n = 2$). In the IFN arm, nine patients died from multiple myeloma itself, and one patient from another cause, but with the myeloma in progress. Four of these 10 patients, however, did not follow the protocol: one patient was never started on IFN, and three discontinued therapy after 1-3 months.

Table 2. Deaths among randomized patients. Status at 1 October 1990

	Interferon ($n = 59$)	No therapy ($n = 61$)
Dead from multiple myeloma after plateau phase therapy according to protocol	5	19
Dead from multiple myeloma after discontinuation of interferon therapy	4	
Dead from other causes while still in plateau phase	2	
Dead from other causes with progressive disease	1	2
Dead from other causes after relapse but with stable disease	1	
Total deaths	**13**	**21**

Dose intensity

The dose intensity was calculated for those 57 patients in whom IFN therapy was started according to the protocol. At the time of the interim analysis, 40% of them were maintained on 90-100% of the original dose, while in 37% a slight to moderate dose reduction (60-90%) was necessary and 9% required a marked dose reduction (20-60%). Eight patients had discontinued therapy entirely.

Toxicity

The proportion of patients on IFN therapy in whom side effects were noted is shown in Figure 2. The most frequently noted toxicity was leukopenia. The majority of patients receiving IFN showed a slight to moderate reduction in the number of circulating white blood cells. In none of the patients was this finding accompanied by a serious infection. Almost half of the patients noted some central nervous system toxicity, usually in the form of a slight to moderate 'chronic fatigue syndrome'. In three patients, such symptoms necessitated the discontinuation of IFN therapy.

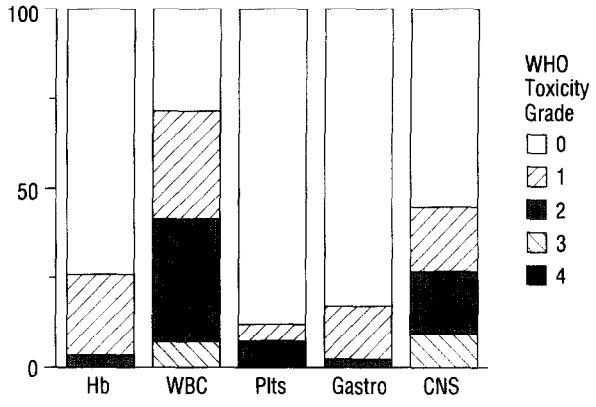

Fig. 2. Toxicity observed among the IFN-treated patients ($n = 57$) up to the time of an interim analysis, performed in October 1990 (median observation time 20 months). Abbreviations: Hb: haemoglobin, WBC: white blood cells, Plts: platelets, Gastro: gastrointestinal toxicity, CNS: central nervous system toxicity, mainly mild forms of the 'chronic fatigue syndrome'.

CONCLUSIONS

The main finding in this interim analysis is a significant prolongation of the duration of plateau phase among the IFN-treated patients, as compared to patients receiving no therapy. Since the number of patients still in plateau phase is small (24 in the IFN arm and nine in the no therapy arm), this difference between the two treatment arms can be expected to remain.

Our findings confirm the results of a previous study [7], but it should be noted that the two studies are different in several respects, e.g., type and length of cytostatic pretreatment, criteria for randomization, dose of IFN.

Since the number of deaths is still small (34 of 120 patients, i.e., 28%), a formal statistical comparison of the survival duration between the two treatment arms has not yet been performed. An analysis of the number and causes of death (Table 2), however, shows that considerably more patients in the no therapy arm than in the IFN arm thus far have died from multiple myeloma or with myeloma in progress (21 versus 13). Continued observation of the patients, analysis of the causes of death, and eventually the statistical comparison of the survival curves for the two treatment arms will show if the observed tendency can be confirmed.

Most patients were able to tolerate IFN therapy, either in the scheduled dose of 5 million units (MU) three times per week (t.i.w.), or with a slight reduction to not less than 3 MU t.i.w., even for rather long periods of time (a few patients are now in their third year of therapy). It is worth noting in this context that the median age of the participating patients was quite high (70 years). For almost half of the patients, however, a more marked reduction was necessary, mainly because of leukopenia and/or because of subjective side effects, similar to a chronic fatigue syndrome.

In conclusion, our interim results indicate that maintenance treatment with interferon alfa-2b during the plateau phase may be an important addition to the therapeutic regimen of patients with multiple myeloma.

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Interferon and Dexamethasone in Multiple Myeloma Patients Refractory to Chemotherapy*

Jesús F. San Miguel, Maria Moro, Juan Bladé, Luciano Guerras, Jose Hernandez, Ramiro Jimenez-Galindo, Fernando Ortega, Marcos Gonzalez

INTRODUCTION

THE TREATMENT of refractory myeloma represents an important and challenging problem [1]. Both *in vitro* and *in vivo* studies have shown that interferons have anti-tumoral activity in myeloma patients [2,3]. Moreover, the combination of alpha interferon and prednisone has an additive inhibitory effect on myeloma colony formation [4]. Based on these observations, we conducted a pilot study in order to investigate the effectiveness of the combination of alpha interferon and high-dose dexamethasone in patients with refractory myeloma [5].

PATIENTS AND METHODS

Thirty-two patients (15 male, 17 female) with refractory multiple myeloma were included in the study: nine cases were primarily resistant; 17 cases were secondarily resistant after an initial response; and six cases had relapsed on cessation of therapy.

The treatment schedule was as follows: a) induction (3 months) - interferon alfa-2b 4 million units (MU)/m^2 subcutaneously (s.c.) three times per week (t.i.w.) and 4-day pulses of 25 mg/m^2/day of dexamethasone with intervals of 4 days during the first month, 10 days during the second month, and 15 days during the third month. Thus, a total of eight pulses were given during this induction phase; b) maintenance - interferon alfa-2b 2 MU/m^2 s.c. t.i.w. and dexamethasone 25 mg/m^2 for 4 days every 3 weeks.

Criteria for objective response (OR) included a 50% decrease in serum M-component and/or > 90% decrease in light chain proteinuria; disappearance of plasmocytomas; resolution of anaemia and hypercalcaemia; improvement in performance status (ECOG); and no increase in lytic lesions. A partial response (PR) included a 25-50% reduction in serum M-component plus the other criteria as for OR.

Lymphocyte subsets (CD4, CD8) were determined in 14 patients by flow-cytometry before and 3 months after initiation of interferon therapy.

RESULTS

Of the 32 patients included in the study, 22 completed the 3 months' induction therapy, six were considered early deaths (all with poor performance status - PS 3 or 4), and in four patients there was a major protocol violation.

Response

Of the 22 evaluable patients, seven achieved an OR (31.8%), eight a PR (36.4%) and the remaining seven (31.8%) were treatment failures. Four of the seven OR patients showed a reduction in bone marrow plasma cells to less than 5%. Follow up of the seven patients with OR shows that four remain in remission on maintenance treatment at 20+, 17+, 6+ and 4+ months, respectively, while the other three relapsed after 6, 12 and 14 months. Three of the eight patients with PR remain stable at 22+, 13+ and 10+ months, respectively.

Response to treatment was independent of the duration of disease prior to study entry, previous treatment, age, sex, M-component and the reason for inclusion in the protocol. Indeed, a high proportion of responses (five out of nine) were found among primarily resistant patients. On the other hand, performance status clearly influenced the response.

Interestingly, five out of 11 patients who were previously refractory to a treatment regimen comprising similar high-dose dexamethasone together with vincristine, BCNU and doxorubicin responded to the interferon/dexamethasone combination.

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