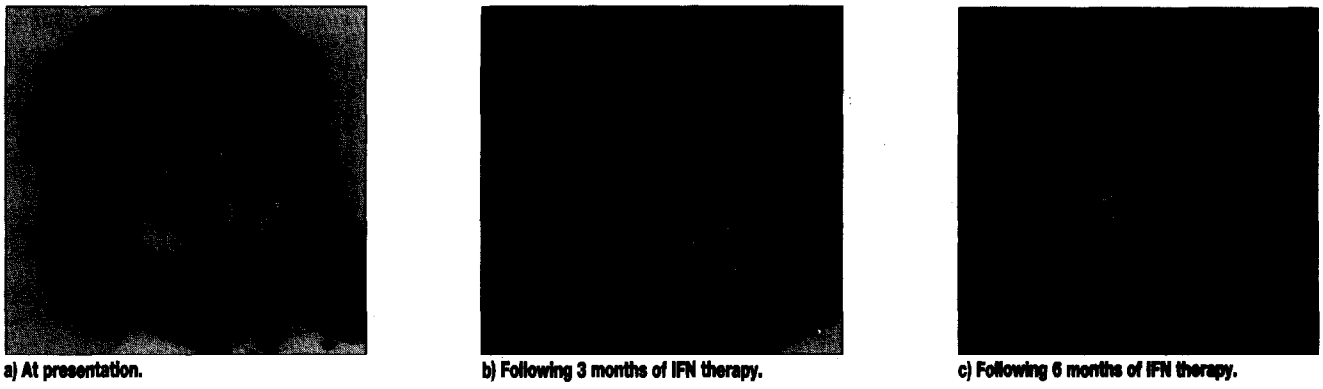

Fig. 1. a) At presentation; b) following 3 months of interferon therapy; c) following 6 months of interferon therapy.

remains in continuous CR on a maintenance dose of 5 MU t.i.w. (Fig. 1).

All three patients had adverse reactions, which consisted largely of flu-like symptoms, mild gastrointestinal discomfort and minor weight loss. All these adverse reactions were transient. No patient had to discontinue treatment as a consequence of adverse effects.

CONCLUSIONS

Based on the current literature review and our own limited experience, alpha interferon appears to be a highly effective treatment modality in advanced CTCL [6]: further studies are desirable.

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Interferon Alfa-2b with VMCP compared to VMCP alone for Induction and Interferon Alfa-2b Compared to Controls for Remission Maintenance in Multiple Myeloma: Interim Results

Heinz Ludwig, Amos M. Cohen, Heinz Huber, David Nachbaur, Walter F. Jungi, Hansjörg Senn, Peter Günczler, Johannes Schüller, Sándor Eckhardt, Heinz L. Seewann, Franco Cavalli, Elke Fritz and Michael Micksche

The present trial was designed to evaluate whether interferon (IFN) combined with standard induction chemotherapy and/or interferon remission maintenance treatment improve treatment results in patients with multiple myeloma. Up to now 89 patients have received IFN plus vincristine/melphalan/cyclophosphamide/prednisolone (VMCP) as induction therapy, and 86 conventional VMCP. The proportion of patients with progressive disease was significantly lower ($P < 0.005$) under IFN + VMCP as compared to the VMCP treatment group. Survival times were significantly longer ($P < 0.02$) after IFN + VMCP induction therapy than after VMCP alone. In the second phase of this investigation, 33 progression-free myeloma patients were assigned to receive IFN as maintenance therapy, and 41 patients served as untreated controls. Patients maintained with IFN showed a tendency towards increased progression-free survival. Haematological side effects were observed significantly

more often in patients receiving IFN, with more severe haematological toxicity in patients on the combined IFN + VMCP regimen and an increased number of patients with mild haematological toxicity in the group maintained with IFN. Other side effects, such as fever and fatigue, remained within tolerable limits. In conclusion, the preliminary results of this current clinical trial indicate significant advantages of combined IFN + VMCP induction treatment in terms of reduced disease progression and prolonged survival and possible benefits of IFN maintenance therapy in patients with multiple myeloma.

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INTRODUCTION

IN MULTIPLE MYELOMA, single-agent treatment with human alpha interferon, natural or lymphoblastoid, induces remissions in about 20% of previously untreated patients [1]. This response seems to depend on the stage and aggressiveness of the disease and possibly on the paraprotein isotype as well. It is significantly lower for beta and gamma interferon than for alpha interferon [1].

Only little is known about the exact mechanisms of interferon (IFN) action in multiple myeloma, but it has been shown that IFN directly inhibits the growth of myeloma stem cells [2] and myeloma cell lines [3] and that *in vitro* it acts synergistically when combined with certain cytostatic drugs [4].

Interferon-induced toxicity is dose-dependent and usually remains tolerable to the patients, provided the applied doses are moderate [5]. Moreover, the toxicity profile of IFN overlaps only partially with the side effects of the cytostatic drugs routinely used in the treatment of multiple myeloma. It is to be expected, therefore, that an induction treatment consisting of a combination of IFN and cytostatic drugs may be beneficial to patients with multiple myeloma. In addition, the minimal residual disease in responsive patients may be successfully prevented from progressing by administering IFN as maintenance therapy. We have been evaluating both hypotheses in a multinational prospective randomized clinical trial. This is an interim report of the current study.

MATERIAL AND METHODS

Patients

Up to now 197 patients with multiple myeloma (95 from Austria, 74 from Israel, 23 from Switzerland, and five from Hungary) have been entered into the study. Their characteristics are shown in Table 1.

Table 1. Patient characteristics

	Induction		Maintenance	
	IFN + VMCP	VMCP	IFN	None
Cases *n*	99	98	33	41
Treatment cycles *n* or months				
Median	6	6	7	8
Range	1-11	1-12	1-19	1-20
Sex				
Male	46	52	15	23
Female	53	46	18	18
Age (years)				
Median	64	63.5	62	62
Range	34-86	31-84	34-80	42-80
Disease stage				
I	8	15	6	5
II	42	44	11	20
III	49	39	16	16
M-component				
IgG	60	61	15	22
IgA	19	20	10	10
IgD	4	–	1	2
IgM	1	–	–	–
Light chain	10	11	3	5
Non-secretory	5	6	4	2
Kappa/lambda	65/34	69/29	26/7	32/9
Pretreatment				
IFN + VMCP			17	24
VMCP			16	17

Induction treatment

As induction therapy all patients received VMCP chemotherapy (vincristine 1.4 mg/m² intravenously (i.v.) on day 1, melphalan 15 mg/m² i.v. on day 1, cyclophosphamide 450 mg/m² i.v. on day 1, and prednisolone 40 mg/m² orally (p.o.) on days 1-7 and 20 mg/m² p.o. on days 8-14) at 4- to 6-week intervals. If assigned to the VMCP treatment group, this was the sole therapy. Patients assigned to IFN + VMCP concomitantly received 2 million units (MU)/day recombinant interferon alfa-2b (Schering-Plough International, USA) five times a week throughout the duration of cytostatic chemotherapy.

Randomization to either IFN plus VMCP or VMCP was performed centrally by stratifying according to treatment centre, disease stage, paraprotein isotype, and renal function.

Of the 99 patients randomized to receive IFN plus VMCP, two refused treatment, seven have not yet completed the minimal treatment period of 4 weeks, and one died from treatment-unrelated causes within days after the start of therapy. Thus, 89 patients are currently evaluable for treatment

Correspondence to: H. Ludwig.
H. Ludwig is at the 1st Department of Medicine and Medical Oncology, Whilhelminenspital, Montleartstr. 37, A-1160 Vienna, Austria.
A. M. Cohen is at the Department of Medice B, Hasharon Hospital, Petah-Tiqva, Israel, H. Huber and D. Nachbaur are at the University Department of Medicine, Innsbruck, Austria, F. Jungi and H. Senn are at the Department of Medicine C, Kantonspital, St. Gallen, Switzerland, P. Günczler and M. Micksche are at AESCA Ltd, Traiskirchen, Austria, J. Schüller is at the 1st Department of Medicine, Rudolfstiftung Hospital, Vienna, Austria, S. Eckhardt is at the National Institute of Oncology, Budapest, Hungary, L. Seewann is at the III Department of Medicine, Hospital Graz, Austria, F Cavalli is at the Division of Oncology, Ospedale San Giovanni, Bellinzona, Switzerland, E. Fritz is at the 1st Department of Medicine and Medical Oncology, Wilhelminenspital, Vienna, Austria.

response. In the VMCP treatment arm, 98 patients have been entered; 10 never started therapy and two have been under observation for less than 4 weeks, leaving 86 evaluable patients.

Response

Response to treatment has been evaluated according to the Southwestern Oncology Group criteria [6]. In the case of complete remission (CR), treatment was continued for three additional cycles; in the case of partial remission (PR), six further cycles were added. If the disease remained stable under therapy, treatment was continued for a total of nine chemotherapy cycles. Disease progression resulted in discontinuation of the applied therapy and termination of the patient's participation in the study.

Maintenance treatment

After completion of chemotherapy, 74 patients have entered the second phase of this investigation. Thirty-three were assigned to receive 2 MU interferon alfa-2b three times a week and 41 were assigned to act as controls without maintenance therapy (None). Randomization included stratification according to treatment centre, mode of induction therapy (IFN plus VMCP versus VMCP), and type of response (CR, PR or stabilization). All patients in both groups were evaluable for maintenance success.

Statistical analysis

Comparisons between groups were performed by means of the non-parametrical Kruskal-Wallis test for continuous data. For frequencies, the chi-square test or Fisher's exact test were applied as appropriate. All data concerning durations were processed according to Kaplan and Meier and censored if necessary. For these time-related data, significance of differences was determined by means of the log-rank test.

RESULTS

Induction treatment

Response to treatment (CR and PR) was comparable in both groups, although slightly higher rates were observed in the IFN plus VMCP than in the VMCP treatment arm. The proportion of patients with progressive disease was significantly lower ($P < 0.005$) on IFN plus VMCP as compared to the VMCP treatment group, who showed four times as many cases of disease progression (Table 2).

Table 2. Response to treatment

	Induction therapy		Maintenance therapy	
	IFN/VMCP	VMCP	IFN	None
Complete response	21 (23.6%)	16 (18.6%)	1 (3.0%)	-
Partial response	41 (46.1%)	38 (44.2%)	-	-
Stable disease	21 (23.6%)	10 (11.6%)	20 (60.6%)	21 (51.2%)
Progression	6 (6.7%)	22 (25.6%)	12 (36.4%)	20 (48.8%)

Analyses of response conditions revealed a marked influence of the patient's stage of disease on his response to IFN plus VMCP treatment. Patients with less advanced disease (myeloma stages I and II) showed clearly improved response rates to IFN plus VMCP therapy as compared to VMCP chemotherapy alone (Fig. 1).

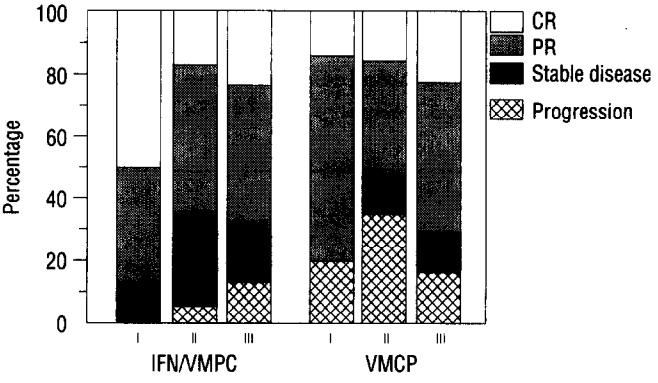

Fig. 1. Response to induction treatment stratified by disease stages. The beneficial effects of combined IFN plus VMCP therapy show more clearly in patients with disease stages I or II than in cases with advanced myeloma (stage III).

The median time necessary to achieve CR has been similar in both treatment arms, i.e. 3.5 and 2.8 months for IFN plus VMCP and VMCP, respectively. The median progression-free survival has been somewhat longer when induced by IFN plus VMCP (20.3 months) than after VMCP induction therapy (16.1 months), but this difference has not yet reached statistical significance.

Survival times, on the other hand, were distinctly and significantly ($P < 0.02$) longer after IFN plus VMCP induction therapy than under VMCP alone. After 33 months, cumulative survival in the IFN plus VMCP arm has not yet reached the 75% mark, while in patients who were treated with VMCP chemotherapy only, the 50% cumulative survival has amounted to only 31.5 months (Fig. 2).

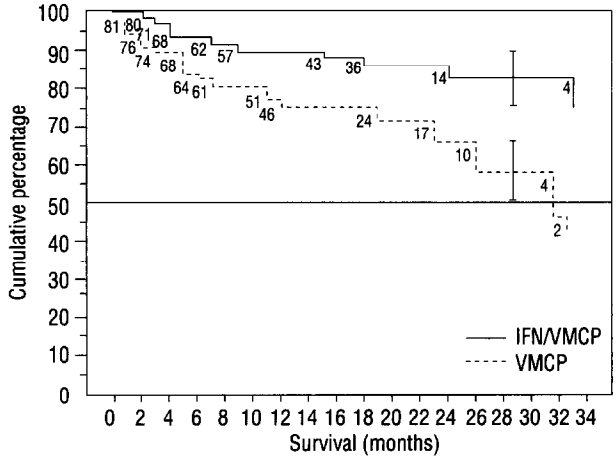

Fig. 2. Cumulative percentage of survival from the start of induction therapy. Survival in the entire patient subgroup (irrespective of response to treatment) is significantly longer ($P < 0.02$) after treatment with IFN plus VMCP than after VMCP chemotherapy alone. (Inserted small numbers = numbers of patients at risk. Bars = standard error at the tail end of the curves.)

Severe haematological toxicity (WHO grades III and IV) was observed significantly more often ($P < 0.001$) in the combined IFN plus VMCP treatment arm than under VMCP (Table 3).

Because of this side effect on the bone marrow, IFN had to be discontinued in three patients and temporarily suspended in 12 cases. Fever, a common side effect of IFN during the initial 2-3 weeks of treatment, was more frequently observed ($P = 0.075$) in patients treated with the combined IFN plus VMCP regimen. None of the other documented side effects showed significant differences between the two treatment arms (Table 3).

Table 3. Treatment side effects and symptoms during observation

	Induction therapy		Maintenance therapy	
	IFN/VMCP	VMCP	IFN	None
Haematological toxicity I & II	74 (83.2%)	62 (72.1%)	20 (60.6%)	13 (31.7%)
Haematological toxicity III & IV	40 (44.9%)	15 (17.4%)	0	2 (4.9%)
Fever	47 (52.8%)	30 (34.9%)	10 (30.3%)	5 (12.2%)
Infections	28 (31.5%)	25 (29.1%)	3 (9.1%)	6 (14.6%)
Nausea	33 (37.1%)	36 (41.9%)	7 (21.2%)	6 (14.6%)
Fatigue	70 (78.7%)	55 (64.0%)	14 (42.4%)	9 (22.0%)
Alopecia	24 (27.0%)	33 (38.4%)	1 (3.0%)	0
Neurological, psychological	21 (23.6%)	24 (27.9%)	2 (6.1%)	0

Maintenance treatment

So far, 74 patients have entered the maintenance phase. Thirty-three have been randomized to IFN maintenance therapy, and 41 to serve as controls. Interim analysis shows that in both groups 21 patients have remained free of progressive disease. Similar to the results of induction therapy, however, disease progression has, up to now, occurred more often in the unmaintained control group (48.8%) than in patients on IFN maintenance therapy (36.4%; Table 2). The median progression-free observation time has been 13.1 months in the IFN-maintained patient group as compared to 8.0 months in patients without maintenance therapy (Fig. 3). This latter difference, however, has not yet reached statistical significance. Although only seven patients have so far died during the maintenance phase (two under IFN, five untreated), the survival curves suggest differences ($P = 0.125$) in favour of IFN maintenance therapy (data not shown).

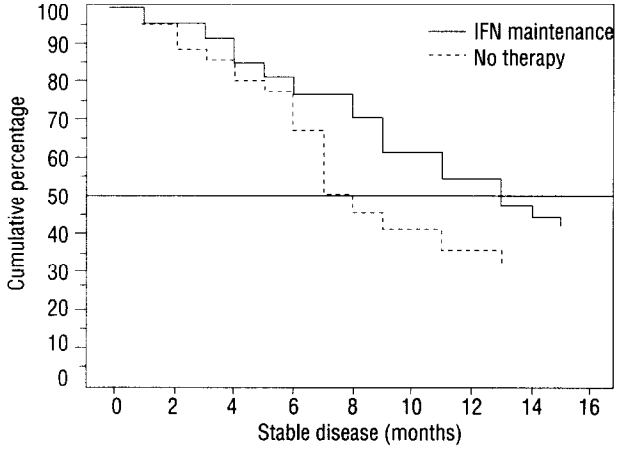

Fig. 3. Progression-free survival during the maintenance phase. Patients maintained with IFN have remained progression-free for a median time period of 13.1 months; without maintenance therapy, the respective period was 8.0 months.

During the maintenance phase, IFN caused mild haematological toxicity; i.e., WHO haematological toxicity stages I and II were observed significantly more often ($P < 0.05$) in the IFN treatment group than in controls (Table 3). Fever and fatigue occurred in a higher number of cases maintained with IFN, but these differences have so far failed to reach the threshold of statistical significance.

Global evaluation

Treatment success has been evaluated in terms of progression-free survival times for all combinations of treatment regimens investigated in this clinical trial (IFN plus VMCP/IFN, IFN plus VMCP/none, VMCP/IFN, VMCP/none). The cumulative percentages of these subgroups are shown in Figure 4. It emphasizes that progression-free survival is not only a result of maintenance treatment, but also a continued effect of the induction therapy. The beneficial influence of IFN during induction treatment seems to extend into the maintenance phase, even if IFN treatment had been terminated. On the other hand, relapse was likely to occur sooner in patients who had never received any IFN at all (VMCP/None). The intervals between the achievement of response and randomization into a specific arm of the maintenance trial were comparable in all four subgroups.

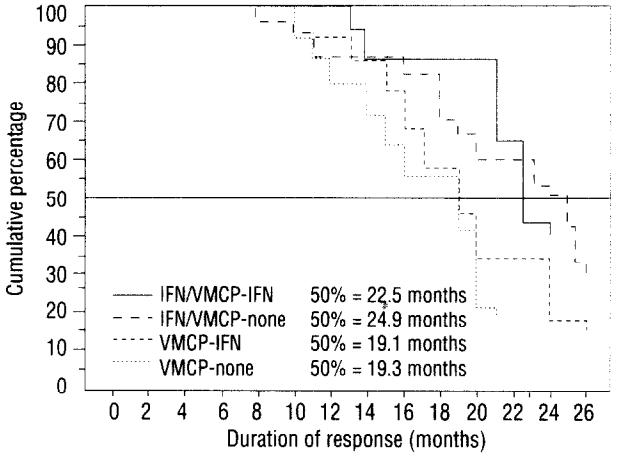

Fig. 4. Progression-free survival as a combined effect of both induction and maintenance treatment. Depending on the treatment regimens during induction and maintenance phase, the median time period of progression-free survival varies. The benefits of IFN during the induction phase seem to persist even without further maintenance treatment. As expected, the shortest median progression-free survival is observed in the treatment group that has received no IFN at all.

DISCUSSION

The interim analysis of this current study yields interesting results. Addition of IFN to the conventional induction chemotherapy regimen led to a remarkable and statistically significant reduction of progressive disease. This effect and the slightly increased response rates in the IFN plus VMCP treatment arm were most pronounced in patients with low to moderate tumour mass.

These observed beneficial effects of IFN in the early treatment phase of myeloma confirm previous similar reports. In our preceding pilot study on recombinant interferon alfa-2c in combination with VMCP, we observed slightly higher response rates on the combination regimen than on chemotherapy alone [7]. Similarly, ongoing investigations in Sweden indicate a higher efficacy of combined IFN-melphalan-prednisone regimens in terms of response rates as compared to melphalan-prednisone alone [8]. Increased response rates were also observed in an Eastern Cooperative Oncology Group study, which gave IFN in combination with a five drug (VMCP plus BCNU: VBMCP) chemotherapy regimen [9]. Under this treatment mode, objective responses could be induced in 80% of 54 previously treated patients. Complete remissions – defined as disappearance of the M-component and the normalization of plasma cell counts in the bone marrow – were observed in 26% of the treated patients. This seems to be a remarkable improvement over the 10% complete response rate obtained with chemotherapy alone in historical controls [9].

Another important result of combining VMCP induction therapy with IFN was the significant prolongation of survival time in patients who had received IFN plus VMCP. Of course, this finding needs to be confirmed by the final evaluation of all patients participating in this investigation. Should improved overall survival remain a statistically significant main result of this clinical trial, IFN would be likely to become an integral part of induction treatment regimens for multiple myeloma.

The reported benefits of combined IFN plus VMCP – reduced disease progression and improved survival – was achieved at the cost of some additional toxicity, which we consider acceptable. Although episodes of severe haematological toxicity (WHO grades III and IV) were seen significantly more often in the combined treatment arm, IFN therapy had to be interrupted in only a minority of patients and discontinued only in exceptional cases. As expected, IFN-induced fever was a common finding at the onset of treatment, but normally subsided after 2-3 weeks of IFN therapy.

Two facts may explain the relatively mild toxicity of IFN observed in this clinical trial: firstly, the doses of IFN given to our myeloma patients were lower than those of IFN/chemotherapy combination protocols used in the treatment of other types of cancer [10]. Secondly, our induction treatment protocol provides for prednisolone to be given during 14 days of each chemotherapy treatment cycle and corticosteroids have been shown to reduce IFN toxicity without affecting treatment efficacy [11].

Maintenance therapy has not yet been applied to a sufficient number of patients or for a long enough period to allow definitive conclusions. However, the current results of fewer occurrences of relapse and apparently longer survival times are in accordance with an Italian study in which IFN maintenance treatment resulted in a significant improvement of progression-free survival as well as in significantly increased overall survival [12, 13]. A number of ongoing clinical studies are looking at this same question [14, 15].

Toxicity of IFN maintenance treatment – relatively mild bone marrow suppression, fever and fatigue – was negligible in the majority of cases. In some elderly patients, however, neurotoxic side effects may necessitate discontinuation of treatment.

In conclusion, the preliminary results of this current clinical trial indicate significant advantages of combined IFN plus VMCP induction treatment in terms of reduced disease progression and prolonged survival. It also appears that relapse may be further reduced by the use of IFN as maintenance treatment. However, in order to exploit the benefits of IFN to their full extent, more detailed information is needed on the mechanisms of IFN action in myeloma. For example, it is still virtually unknown whether the direct anti-proliferative effects of IFN [16], its immunomodulatory capacity [17, 18], its hypothetical role in the production of positive or negative growth factors [19], or other mechanisms [20] play a decisive role in successful treatment of multiple myeloma. Until this knowledge becomes available, the potential value of this biological response modifier in treating myeloma patients has to be derived by means of empirically designed treatment regimens. This interim report is intended hopefully to contribute to this important clinical aim.

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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.

Correspondence to J. Westin.
J. Westin is at the Haematology Section, Department of Medicine, University Hospital, S-221 85 Lund, Sweden.
A. Cortelezzi is at the Department of Hematology, University of Milan, Italy, M. Hjorth is at the Department of Medicine, Lidköping Hospital, S Rödjer is at the Department of Medicine, Östra Hospital, University of Göteborg, I Turesson is at the Department of Medicine, Malmö General Hospital, University of Lund, and G. Zador is at Schering-Plough AB, Stockholm, Sweden.

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