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IMPACT OF INTERFERON AT INDUCTION CHEMOTHERAPY AND MAINTENANCE TREATMENT FOR MULTIPLE MYELOMA

Preliminary results of a multicenter study by the Italian Non-Hodgkin's Lymphoma Cooperative Study Group (NHLCSG)

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In 1990 the Italian Non-Hodgkin's Lymphoma Cooperative Study Group (NHLSG) started a multicenter study on the role of interferon (IFN) in multiple myeloma (MM). The schedule of treatment was based on the assumption that melphalan plus prednisone (MP) would be better for good-prognosis patients, whereas poor-prognosis patients would benefit from polychemotherapy. Accordingly, IFN was included randomly for the induction treatment of good-prognosis patients and randomly as maintenance of the response achieved in both groups. Up to now 78 patients of the 124 enrolled have completed the induction treatment and are evaluable for response and response duration. The overall response rate was 59%. Sixty-two percent of good-prognosis patients obtained objective response, 9/14 (64%) with MP and 9/15 (60%) with MP + IFN. Up to now, with a median follow-up of 9 months from the evaluation of response, no difference has been recorded between the maintenance and no maintenance groups on relapse rate, neither in good- nor in poor-prognosis patients.

Interferon (IFN) has proved to be effective in multiple myeloma (MM) both in vitro and in vivo (1). Several studies investigated the combination of IFN and chemotherapy (2–5) or employed IFN as maintenance therapy during remission (6, 7). This report presents preliminary data from the ongoing randomized trial of the Italian Non-Hodgkin's Cooperative Study Group (NHLSG) on melphalan plus prednisone (MP) with or without IFN and on the use of IFN as maintenance in patients with MM.

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Material and Methods

Between June 1990 and October 1992, 124 patients with MM diagnosis were enrolled into the study. Seventy-eight of them have completed induction treatment and are presently evaluable for response assessment and for response duration. Twelve patients were not evaluated, 5 because of protocol violation, 3 of missing data, 3 of poor compliance and 1 because of myocardial infarction at the first cycle treatment. Thirty-four patients are still under induction treatment. Symptomatic patients were stratified according to prognostic factors in low- and high-risk groups (8). The low-risk (LR) patients were randomly allocated to an arm receiving melphalan, 2.5 mg, and prednisone, 25 mg/m^2 daily p.o. (MP), or to MP plus IFN alpha 2b, 3 million units s.c. trice weekly (MP + IFN) for 9 months. High-risk (HR) patients received polychemotherapy randomly: vincristine, 1 mg day 1, melphalan 6 mg/m^2 p.o. cyclophosphamide 125 mg/m^2 p.o. and prednisone 60 mg/m^2 i.v., days 2 to 6 (VMCP) or vincristine 1 mg and peptichemio 80 mg/m^2 day 1 and pred-

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nisone 60 mg/m^2 i.v., days 1 to 5 (VPP). (Peptichemio is a peptidic compound containing m-L-phenylalamine mustard). These treatments were discontinued after 6 monthly cycles. Patients with renal failure were treated with vincristine 2 mg and doxorubicin 30 mg/m^2 day 1 and prednisone 60 mg/m^2 i.v. days 1 to 5 for 6 courses (VAP). Patients in both the HR and the LR risk groups responding to the induction treatment were randomized to maintenance with IFN, 3 million units twice weekly or observation without IFN, until relapse. The response criteria were those of the Chronic Leukemia Myeloma Task Force. Survival curves were plotted by the Kaplan–Meier method from the start of induction treatment and disease-free survival time from the end of induction treatment with comparison by the log-rank test. Prognostic factors were computed by univariate and multivariate (Cox model) analysis (MPS-Metrika Statistical Software, Verona-Italy).

Results

Seventy-eight patients had completed induction treatment and were evaluable for preliminary results. Characteristics of the patients are listed in Table 1. The treatment groups were well balanced according to prognostic factors, 14 patients being treated with MP and 15 with MP + IFN and 23 and 18 with VMCP and VPP respectively. Table 2 shows the response rate according to treatment. LR patients treated with MP obtained a 64% objective response as compared with 60% obtained by MP + IFN treatment. Up to this analysis 38/46 patients who had obtained objective response were randomized to maintenance with IFN, (n = 22) or nothing, (n = 16). The median observation time from the end of induction was 9 months (range 2–32). Thirty-one percent of the patients observed without IFN relapsed vs 50% of the patients maintained with IFN, in a median time of 12 and 8 months respectively. The toxicity of MP + IFN was greater than of MP due to flu-like syndrome occurring in 34% of patients and to leukopenia which, however, did not increase the rate of infections.

Table 1

Patient characteristics. No. of patients

Characteristic	Low-risk		High-risk		'B' VAP
	MP	MP + IFN	VMCP	VPP	
No.	14	15	23	18	8
Sex m/f	4/10	4/11	11/12	10/8	5/3
Age, years	66	65	66	65	59
IgA	4	4	7	5	1
IgG	9	10	12	9	3
IgD	–	–	1	1	1
BJ myeloma	1	1	3	3	3
Stage					
1	8	5	3	1	–
2	2	4	7	7	2
3	4	6	13	10	6
Low-risk	14	15	–	–	–
High-risk	–	–	23	18	8

Abbreviations: MP, melphalan plus prednisone; IFN interferon; VMCP, vincristine, melphalan, cyclophosphamide, prednisone; VPP, vincristine, peptichemio, prednisone, VAP, vincristine, doxorubicin, prednisone.

Table 2

Response rate. No. of cases (%)

Response	Low-risk		High-risk		'B' VAP
	MP	MP + IFN	VMCP	VPP	
> 50%	9(64)	9(60)	16(69)	9(50)	3(37)
< 50%	2	2	4	6	2
Stable disease	1	1	–	–	1
Progression	2	3	3	3	2
Total	14	15	23	18	8

Discussion

Of the two major questions posed in this study, whether IFN might improve the response to conventional treatment with melphalan and prednisone and prolong the response duration when given as maintenance, we are at present able to answer only to the first one. Concerning the second question our results are too preliminary to draw any conclusions because of the large number of different chemotherapeutic programs used, even though no improvement in the duration of response with the use of IFN as maintenance treatment has been noticed until now.

In our study IFN did not improve the response rate when added to MP. This result is in agreement with the results of Cooper et al. (3) and Corrado et al. (4). Similar to these studies we used concomitant delivery of IFN with melphalan and prednisone. The schedule used in our trial with MP given continously rather than intermittently seemed to have no influence on the response rate. Kyle et al. (5) on the contrary reported promising results alternating polychemotherapy with IFN. However, also with melphalan and prednisone the sequential use of IFN was found effective (2).

In conclusion it would appear that the major problem may be the modality of administration of IFN. The present study does not confirm an advantage of concomitant administration of IFN alfa-2b with standard melphalan and prednisone as induction therapy for patients with multiple myeloma.

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