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Two dosage interferon-α2b maintenance therapy in patients affected by low-risk multiple myeloma in plateau phase: a randomized trial

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Abstract

Background and Objective. **The role of interferon (IFN) in the remission phase of multiple myeloma (MM) is still an open question, particularly for its scheduling and the subset of patients who could benefit from this approach. The present randomized multicenter study was designed to compare two schedules of IFN maintenance therapy in order to assess the difference in effectiveness and tolerance.**

Design and Methods. **This prospective randomized multicenter study was attempted to assess the best schedule of IFN administration in the maintenance treatment of MM in *plateau* phase with regard to progression free survival (PFS) and toxicity. The second aim was defining the difference between the two schedules in overall survival (OS) and identifying the critical dose of IFN therapy needed to prolong *plateau* phase and survival. We enrolled 52 patients affected with low-risk MM (i.e. with serum β2-microglobulin < 6.0 mg/L and serum albumin > 3.0 g/dL); 27 patients (group A) were randomly assigned to receive IFNα-2b 3 megaunits (MU) subcutaneously three times a week and 25 patients (group B) 3 MU/day until disease progression.**

Results. **Median progression free survival (PFS) was 11.9 months in group A and 38.3 months in group B (p= 0.0038). Median survival was 63.2 months in group A and 61.9 months in group B (p= 0.489). However, those patients who were given an IFN dose ≥ 30 MU/month experienced a significantly longer PFS and survival than the other patients. Seventeen patients (32.7%) discontinued therapy and sixteen patients (30.8%) reduced IFNα-2b dose because of severe side effects without having a significant difference between the two schedules.**

Interpretation and Conclusions. **Our results show that patients treated with IFNα 3 MU/day had a significantly longer remission duration than patients treated with IFNα 3 MU three times weekly. Moreover, an IFN dose is probably critical for obtaining a longer survival in patients affected with low-risk MM. Since the patients' discomfort during a IFN maintenance therapy was frequently experienced the quality of their lives should be carefully taken into account.**

Key words: interferon, maintenance therapy, multiple myeloma, survival

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Although much progress has been made in the knowledge of biologic and prognostic factors of multiple myeloma (MM),[1] survival has not significantly changed since the melphalan-prednisone combination was employed.[2-4] Indeed, by introducing multidrug regimens, response rate has improved, but not survival.[5-7]

Interferon (IFN) used as single induction agent[8,9] or in combination with conventional chemotherapy[10] did not substantially change MM prognosis.

High-dose therapy followed by allogeneic bone marrow transplantation was able to cure some patients,[11-12] but it can be performed only on a small group of patients; on the contrary, autologous stem cell transplantation can be widely performed and is now a standard procedure for treatment patients with MM[13,14] although the relapse rate remains high.

Maintenance chemotherapy has not shown advantages in prolonging survival and a higher incidence of secondary leukemia was found.[15] On the contrary, maintenance with IFN significantly prolonged response duration but not overall survival in patients who had responded to induction chemotherapy.[16-19] Therefore the role of IFN in the remission phase of MM is still an open question, particularly for the schedule and the correct identification of the subset of patients who could benefit from this approach.

The present randomized multicenter study was designed to compare two schedules of IFN maintenance therapy in order to assess the difference in effectiveness and tolerance.

Materials and Methods

Study design

This prospective randomized multicenter study was attempted to assess the best schedule of IFN administration in the maintenance treatment of MM in *plateau* phase with regard to progression-free survival (PFS) and toxicity; the second aim was defining the difference between the two schedules in overall survival (OS) and identifying the critical dose of IFN therapy needed to prolong *plateau*

phase and survival.

We enrolled patients affected by low-risk MM (see below) diagnosed according to *Chronic Leukemia-Myeloma Task Force* criteria,[20] with the following characteristics: disease at any stage according to Durie and Salmon;[21] no age limits; performance status (PS) < 2 according to *World Health Organization* (WHO); normal renal and hepatic function and no cardiac failure.

After oral informed consent, patients were randomly assigned to receive IFNα-2b (Intron-A, Schering-Plough Corp.) 3 megaunits (MU) three times a week (group A) or 3 MU/day (group B), subcutaneously, until disease progression occurred. IFNα-2b was administered on an outpatient basis and acetaminophen was used to reduce influenza-like symptoms at the discretion of the patients. Dose reduction was carried out according to WHO criteria; therapy discontinuation was provided only for grade III-IV WHO side effects, patient refusal or disease progression. However, the schedule (daily or intermittent administration) was maintained and the results were considered on an intention-to-treat basis for the primary end point.

Definition criteria

Low-risk MM was defined according to Bataille *et al*.[22] staging system i. e. patients with serum β2-microglobulin < 6.0 mg/L and serum albumin > 3.0 mg/dL. Response to chemotherapy was assessed according to *Chronic Leukemia-Myeloma Task Force* criteria.[20]

Plateau phase MM was defined as follows: persistent reduction or absence of MM symptoms, steadiness of hematological parameters without the need of transfusion and steadiness of paraprotein during a 3-month observation.

Disease progression was defined according to the following criteria: reappearance or increase of MM symptoms; reappearance or increase of paraprotein greater than 50% or 100% in the serum or in the urine respectively; appearance or increase in lytic bone lesion; serum creatinine > 2.0 mg/dL; serum calcium > 12 mg/dL or appearance of plasmacells in the blood.

Side effects of IFNα-2b were evaluated according to WHO criteria. The planned dose of IFN was 36 MU/month for the group A and 72 MU/month for the group B. The cut-off dose of 30 MU/month is intented for at least 6 months.

PFS was calculated from time of randomization to disease progression and similarly OS was calculated from randomization to death for any events.

Follow-up

Before randomization and every two months thereafter, patients underwent clinical and laboratory examinations including hemocytometric counts, electrophoresis serum and 24-hour urine samples for paraprotein determination, renal and hepatic functions, serum calcium and sβ2m. Every 12 months or when clinically indicated, a bone marrow biopsy and a complete skeletal radiography were performed.

Once disease progression was established during the IFN therapy, subsequent chemotherapy was left at the discretion of the attending physicians. One patient (group A) underwent myeloablative therapy followed by blood progenitor cell rescue; all the other patients were treated with conventional chemotherapy including oral melphalan-prednisone, VMCP, VBMCP, VAD, high-dose dexamethasone or cyclophosphamide regimens. No randomized patient was lost to follow-up.

Statistical methods

The sample size of the population was calculated to ensure a 5% level of significance and a power of 80% if a difference in the probability of PFS was 35% between the two schedules of IFN administration. Randomization was made centrally by using a standard computer program.

The characteristics of the two groups of patients as well as toxicity were compared by using the Mann-Whitney test for continous variables and chi-square test (contingency table) for categorical variables.

PFS and OS estimate were performed by Kaplan-Meier method[23] and compared by using log-rank test. The best cut-off of dose of IFN therapy was empirically pursued using log-rank test to compare the Kaplan-Meier curves of PFS and OS. In order to weight its prognostic value, IFN dose was included in a stepwise Cox regression analysis[24] together with age, PS (0-1 vs 2), stage (I vs II-III), serum β2-microglobulin, serum albumin and bone marrow plasmacells. A p value < 0.05 was considered statistically significant.

Results

Patient population

From January 1989 to December 1994, 196 untreated patients affected by MM were reported in 10 medical departements of the Marche region (Italy). One hundred two patients (52%) were affected by low-risk MM according to the Bataille *et al*.[22] staging system. Five of these patients (4.9%) were excluded because of important concomitant diseases. Twenty patients (19.6%) had stable MM stage I A; since they were not suitable for treatment and were excluded. The remaining 77 patients (75.5%) were available for treatment but 3 of them refused the protocol, 2 died before randomization and 3 others were lost at follow-up. Out of the remaining 69 patients treated, 52 responded to chemotherapy and therefore were randomized for the two different dose of IFN. Out of 52 random-

Table 1. Characteristics of the two groups of patients and comparison.

Characteristics	Total	Group A*	Group B°	p value
No. of patients	52	27	25	/
Age				
median (range)	67.5 (47-85)	66 (51-83)	70 (47-85)	0.117
Sex				
M	24	13	11	0.983
F	28	14	14	
Paraprotein				
IgG	37	20	17	
IgA	9	3	6	0.393
Bence-Jones	6	4	2	
Stage				
I	23	12	11	0.945
II-III	2	15	14	
PS (WHO)				
0-1	28	14	14	0.983
2	24	13	11	
Bone marrow plasma cells (%) – median (range)	41.5 (15-90)	40 (20-83)	49 (15-90)	0.2051
β2 microglobulin (mg/mL) – median (range)	2.4 (1.2-4.8)	2.5 (1.2-4.8)	2.3 (1.3-4.5)	0.486
Albumin (g/mL) – median (range)	4.0 (3.0-5.1)	4.3 (3.0-5.1)	3.8 (3.0-5.0)	0.748
Hemoglobin (g/dL) – median (range)	12.4 (8.6-17.0)	13.0 (8.6-17.0)	12.1 (8.9-16.9)	0.230
Platelets (x10^9/L) – median (range)	195 (69-389)	200 (69-329)	190 (96-389)	0.647
LDH (U/L) – median (range)	238 (125-440)	230 (130-430)	250 (125-440)	0.287

**IFN 3 MU three times a week; °IFN 3 MU/day.*

ized patients, 44 (22 group A, 22 group B) received oral melphalan plus prednisone for seven days,[25] 4 (2 group A, 2 group B) VBMCP regimen[26] and 4 (3 group A, 1 group B) were treated with VAD regimen.[27]

Clinical and laboratory characteristics of the 52 randomized patients are listed in Table 1. Twenty-seven patients were randomly assigned to group A (IFNα-2b 3 MU three times a week) and 25 to group B (3 MU/day). As shown in Table 1, the two groups were comparable for all the considered characteristics.

Progression-free survival

Up to December 1996, with a median follow-up time of 42 months, 31 patients (59.6%) experienced disease progression, 21 (77.8%) in group A and 10 (40.0%) in group B (p= 0.01273). The total median PFS was 24.8 months; in group A the median PFS was 11.9 months and 38.3 months in group B (p= 0.0038) (Figure 1).

PFS of 37 patients given a dose of IFN ≥ 30 MU/month was 34.3 months vs 10.4 months of the 15 patients treated with a lower dose (p= 0.0015; Figure 2).

Overall survival

Eighteen patients (34.6%) died by the time of this report, 11 (40.7%) in group A and 7 (28%) in group B (p= 0.50084). All patients in group A died

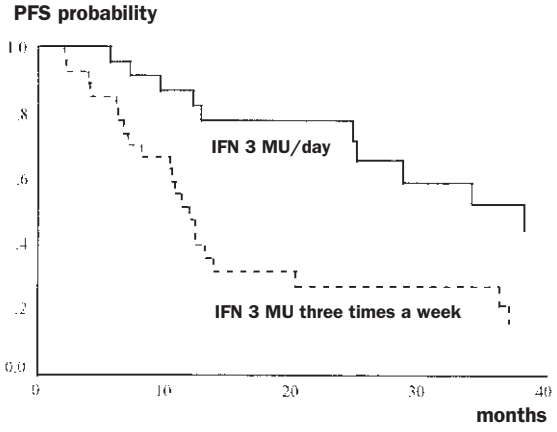

Figure 1. Kaplan-Meier progression free survival (PFS) curves according to the IFN schedule. Patients treated with IFN 3 MU/die had a significantly longer PFS than patients treated with IFN 3 MU three times a week (median PFS 38.3 vs 11.9 months; p = 0.0038).

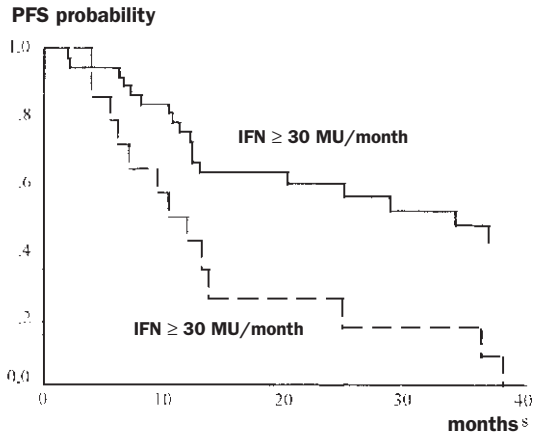

Figure 2. Kaplan-Meier progression free survival (PFS) curves according to the IFN dose. Patients treated with IFN ≥ 30 MU/month had a significantly longer PFS than patients treated with lower dose (median PFS 34.4 vs 10.4 months; p = 0.0015).

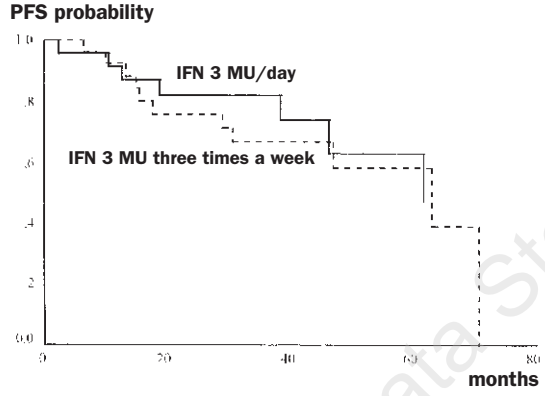

Figure 3. Kaplan-Meier overall survival curves according to the IFN schedule. The difference between patients treated with IFN 3 MU/day and patients treatyed with IFN 3 MU three times a week was not significant.

because of disease progression; on the contrary, in group B, 3 patients died on stable disease (2 cerebral hemorrhages with normal platelet count and 1 cardiac failure).

Total median duration of survival was 63.5 months; in group A survival was 63.2 months and 61.9 months in group B (p= 0.489) (Figure 3). Even if we censored the patients who died on stable disease for causes apparently unrelated to MM, survival was not significantly different between the two groups (p= 0.1126: data not shown). However, comparing those patients given a dose of IFN ≥ 30 MU/month with those treated with a lower dose, the median survival proved to be significantly different (71.0 vs 46.5 months respectively; p = 0.0043; Figure 4).

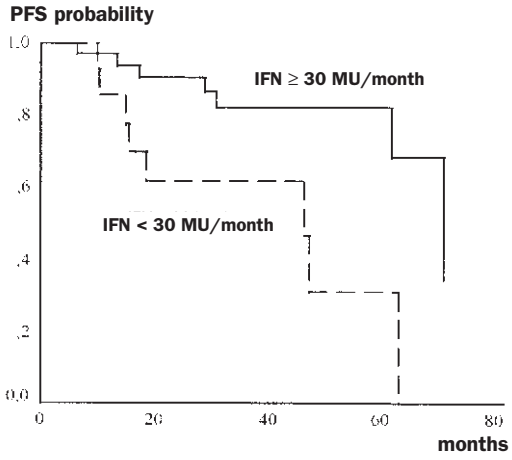

Figure 4. Kaplan-Meier overall survival curves according to the IFN dose. Patients treated with IFN ≥ 30 MU/month had a significantly longer survival than patients treated with lower dose (median survival 71.0 vs 46.5 months; p = 0.0043).

Prognostic factors

Stepwise Cox regression analysis showed that only serum β2-microglobulin and IFN dose affected PFS (Table 2); whereas age, PS (WHO), stage, serum albumin and bone marrow plasmacells did not.

Patients given a dose of IFN < 30 MU/month had a 60% higher probability of disease progression than patients treated with the higher dose of IFN ≥ 30 MU/month (Table 2).

Stepwise Cox regression analysis showed that not only serum β2-microglobulin and age were significantly predictive for longer OS but also IFN dose (Table 2). Indeed, patients given a dose of IFN < 30 MU/month had quite a double risk of death than patients treated with a dose of IFN ≥ 30 MU/month (Table 2).

Toxicity

Fourty-three patients (82.7%) experienced side effects without any difference between the two groups (Table 3). Side effects are shown in detail in Figure 5. Thirty-seven patients (71.2%) received a IFN dose ≥ 30 MU/month; however, 10 patients in group A (37%) and 5 patients in group B (20%) received a IFN dose less than 30 MU/month (Table 3). Sixteen patients (30.8%) reduced the dose of IFNα-2b because of side effects without any difference between the two schedules. The median age of patients who needed reduction of dose was 69 years vs 66 years for patients who did not (p= 0.5718). The main causes of therapy reduction were grade III neutropenia (9 patients), anorexia (4 patients) and fatigue (3 patients).

Seventeen patients (32.7%) discontinued therapy

Table 2. Prognostic factors for PFS and overall survival selected by stepwise Cox regression.

Variables	*Patients at risk*	*p value*	*Relative risk (95% CI)*
Progression-free survival			
β2 microglobulin			
≤ 3 mg/L	30	< 0.001	3.3
> 3 mg/L	22		(2.2-5.5)
IFNα dose			
< 30 MU/month	15	0.0054	1.6
≥ 30 MU/month	37		(1.2-2.4)
Overall survival			
β2 microglobulin			
≤ 3 mg/L	30	0.0017	2.3
> 3 mg/L	22		(1.4-3.9)
Age			
> 65 years	32	0.0260	1.1
≤ 65 years	20		(1.1-1.2)
IFNα dose			
< 30 MU/month	15	0.0230	1.9
≥ 30 MU/month	37		(1.1-3.3)

**confidence interval.*

because of severe side effects without any difference between the two schedules; among these, 13 patients had previously reduced IFN dosage. The median age of patients discontinuing therapy was 73 years compared to 66 years for patients not discontinuing (p= 0.05). The more frequent causes of therapy interruption were anorexia with weight loss (6 patients), toxic neurological effects (4 patients), ischemic heart attack (3 patients), itching (3 patients) and neutropenia (3 patients).

Table 3. Toxicity of the two schedules of IFNα and comparison.

Parameters	*Total pts (%)*	*Group A* pts (%)*	*Group B° pts (%)*	*p value*
Side effects	43 (82.7)	22 (81.5)	21 (84.0)	0.932
Dose reduction	16 (30.8)	7 (25.9)	9 (36.0)	0.843
Therapy discontinuation	17 (32.7)	9 (33.3)	8 (32.0)	0.932
Therapy reduction then discontinuation	13 (25.0)	7 (25.9)	6 (24.0)	0.832
IFN dose < 30 MU/month	15 (28.8)	10 (37.0)	5 (20.0)	0.462

**IFN 3 MU three times a week; °IFN 3 MU/day. Pts: patients.*

Discussion

Interferon is a biological response modifier wich is able to carry on a direct[28,29] and indirect[30-32] antimyeloma activity *in vitro*.

In patients with MM responding to conventional chemotherapy, IFNα maintenance treatment has given conflicting results. Indeed some authors obtained a duration of *plateau* phase significantly longer in IFN treated groups than in unmaintained ones;[16-19, 33] on the contrary, in other trials no difference in the length of *plateau* phase between IFN treated groups and control groups was observed.[34,35] However, survival of the patients treated with IFN was not improved in all the above trials. IFN combined with induction chemotherapy and for maintenance treatment gave disappointing results[36-39]

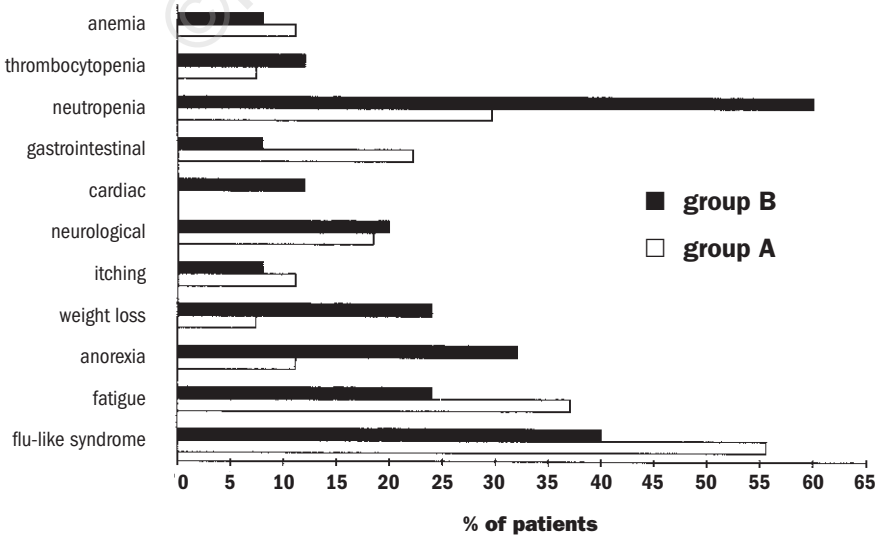

Figure 5. Side effects according the IFN schedule (group B: IFN 3 MU/day; group A: IFN 3 MU three times a week).

except in one study[40] where only IgA and Bence-Jones myeloma patients had a significantly higher rate of remission and longer survival and in another where the same results were obtained in all patients.[41]

Better results have been obtained when tumor size, measured by paraprotein level, was minimal.[17,33] However, the paraprotein level may not be the most accurate measure of tumor size and accordingly, it should not be considered the most important prognostic factor;[22,42] moreover, in the *plateau* phase the kinetic of myeloma cells is rather variable regardless of the paraprotein level.[43]

In vitro and *in vivo* IFN effects on myeloma cells are unclear; indeed, *in vitro* studies showed that IFN stimulated the proliferation of IL-6-dependent myeloma cell lines[44,45] and of freshly explanted myeloma cells in a significant fraction of patients.[46-48] Klein *et al*.[32] demonstrated that, *in vitro*, low dose IFNα promoted myeloma cell growth while a high-dose inhibited plasma cell proliferation. These observations might explain the different results obtained in the above-mentioned trials and would suggest further investigations about factors which more carefully predict *plateau* phase and survival duration.

We supposed that patients with low-risk MM according to Bataille *et al*.[22] were suitable to be treated with IFNα; in this setting we hoped to obtain a long-drawn *plateau* phase with low-dose IFNα. Indeed, all our patients had low tumor burden; moreover, they were responsive to chemotherapy. It has been demonstrated that patients with low tumor burden and/or responsive to chemotherapy maintained an intact NK activity, which can be enhanced by IFN.[49]

Our results demonstrated that patients treated with IFNα 3 MU/day had a remission duration significantly longer than patients treated with IFNα 3 MU three times weekly. In spite of the considerable difference in the *plateau* phase duration, survival was not different in the two randomized groups. This result, even if already described by others[16-19,33-35,50] is surprising and indicates that much more effort should be made to explain this issue.

For this purpose we investigated the role of dosage of IFN maintenance therapy. Our findings showed that patients given a low dose of IFN (e.g. < 30 MU/month) experienced a significantly shorter survival than patients treated with a higher dose; moreover, the latter group of patients obtained a by far longer survival (71 months) than expected (55 months) in the low-risk MM.[22] Many patients (37%) enrolled in schedule A (i.e. IFN 3 MU three times weekly) were not given a sufficient dose of IFN since even a small dose reduction was enough to take down IFN dose under the 30 MU/month (planned dose 36 MU/month); on the contrary, in the B arm (i.e. IFN 3 MU/die), a halved dose was also higher than 30 MU/month (planned dose 72 MU/month). Regardless on this, a 20% of patients treated with schedule B received a IFN dose less than 30 MU/month. We can argue that this high percentage of patients, randomized in the B arm and treated with an insufficient dose of IFN, was responsible for the overlapping in the survival between the two schedules.

It is probable that the dose of IFN may have a heavier weight on OS than the administration schedule; however, IFN therapy could distinguish between patients who can tolerate a higher dose and therefore in a better condition, and who have a better prognosis than those who cannot. This dilemma should be solved by an appropriately designed randomized study.

The toxicity of IFNa was not negligible in both arms without any difference; our results suggest that, in patients affected by MM, a low dose of IFN also give rise to a considerable hematological and extrahematological toxicity; this did not happen in others hematological diseases (i. e. chronic myeloproliferative syndromes) where the IFN compliance is fulfilled for high doses also. This phenomenon can be probably attributed to the advanced age of patients with MM. Indeed, Westin *et al*.[17] also reported severe granulocytopenia in about 25% of patients and chronic fatigue syndrome in about 20% of patients and consequently, the planned dose of 5 MU three times weekly was reduced in many patients. Moreover, Cunningham *et al*.[33] reported therapy discontinuation in about 30% of MM patients mantained with IFN 3 MU three times weekly after autologous transplantation. Therefore, it is evident that IFN, even if at low dose, is not well tolerated in patients affected by MM.

In conclusion, this study suggests that the IFN dose in the maintenance therapy of MM is important in order to obtain a longer *plateau* phase duration; moreover, a critical dose of IFN is probably needed to also obtain a longer survival than expected in patients affected with low-risk MM.[22] Since the toxicity of the two tested schedules is quite similar, we recommend the schedule that contains the higher dose of IFN enabling the administration of a sufficient dose regardless of dose reduction or therapy discontinuation.

Further studies are needed to investigate the role of IFN dose during survival also in other subsets of MM patients.[51] Indeed, this issue is crucial to assess the cost-benefit ratio of IFN maintenance therapy in patients affected by MM whose quality of life could worsen with this therapy.[52]

Contributions and Acknowledgments

M. Offidani: conception and design, patient recruitment and randomization, data handling, day-to-day contact with participants, statistical analysis, data interpretation and writing of the paper.

A. Olivieri: conception, design and writing the study proto-

col, data interpretation and revising the paper. P. Leoni: conception, design, revising the paper and approval the final version to be published. M. Montillo, S. Rupoli, R. Centurioni, F. Alesiani, G. Marchegiani, S. Pieroni, M. Catarini, G. Pelliccia, F. Altilia: clinical assessment, execution of the study. The criteria of the order in which the above names appear are based on the decreasing importance of contribution to the paper except for P. Leoni, who is responsible of the final version of this paper.

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Disclosures

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