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MULTIPLE MYELOMA IN THE ELDERLY: CLINICAL FEATURES AND RESPONSE TO TREATMENT IN 113 PATIENTS

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ABSTRACT

Background. **Considering the conflicting results of the few reports on geriatric MM patients and the increasing relevance of the problem, we analyzed a series of 113 patients over 64 years of age treated with conventional chemotherapy.**

Patients and Methods. **The median age was 71 (range 65-92). Stage IA, IIA, IIIA and IIIB patients numbered 28, 33, 45 and 7, respectively. The M component was IgG in 73 patients (65%), IgA in 30 (26%), IgD in 3 (3%), light chain in 5 (4%); no monoclonal component was detected in 2 (2%) cases. Sixty-three patients showed symptomatic skeletal disease. Melphalan/prednisone (MP) was the first-line treatment in 84 patients (74%). Patients were grouped according to age (>64 ≤74 ; ≥75) in order to carry out analysis.**

Results. **Seventy-eight cases (69%) showed a sizable reduction in the tumor mass; objective and partial response was achieved in 57 (50%) and 21 (19%) patients, respectively. Patients with stage I-II disease fared significantly better than stage III patients (median survival: 70 vs 38 months; p = 0.017). Response to first-line treatment correlated with overall survival; patients with responsive or refractory disease had median survival rates of 64 and 20 months, respectively (p=0.0001).**

Conclusions. **Neither patients above nor below 75 years of age showed any difference in presentation features or in response to treatment. These results suggest that advanced age should not be considered a major obstacle to active treatment.**

Key words: multiple myeloma, chemotherapy, elderly, toxicity

Multiple myeloma (MM) is a relatively frequent neoplasm (1% of all malignancies, 10-15% of hematological neoplasms) whose incidence has steadily increased over the last few decades.[1] It is well known that its occurrence increases after 60 years of age, whereas it is rare under 50. Although a number of recent studies have pointed out several pathophysiological aspects of the disease[2-5] and defined the main prognostic factors,[6-8] few therapeutic improvements have been achieved. In particular, no conventional treatment has proven to be superior to the classic melphalan/prednisone (MP), which has been and still is the *gold standard* for more than 20 years.[9-14] Main therapeutic interest has been focused on relatively young patients (<60-65 years) for whom myeloablative treatment followed by autologous or allogeneic stem cell rescue is producing interesting results.[14-20] The therapeutic approach has not changed for older patients (>65 years) who are not suitable for high dosage treatment; however, this latter category of patients represents the vast majority in all reported series and is expected to increase over time as a consequence of the increased life

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expectancy of the normal population. Since few reports have focused on elderly MM patients,[21-23] we retrospectively studied a series of 113 cases seen in different institutions treating hematologic patients, in order to analyze the presentation features and assess the outcome of treated patients. This is not a randomized study, yet it presents what is currently being done for this group of patients and what can be expected with conventional treatment.

Patients and Methods

One hundred and thirteen consecutive patients without severe heart lung, or liver impairment, treated for symptomatic multiple myeloma from January 1980 to December 1994, were included in the study. Only patients 65 years of age or more at the time of first treatment were considered. Five different institutions provided the clinical data from the patients treated during the last 14 years. Diagnosis was based on the criteria of the *Chronic Leukemia and Multiple Myeloma Task Force*[24] and stage was defined according to Durie and Salmon.[25] We first analyzed the data of the group as a whole and then separately on the basis of age, splitting them into two subgroups (≥ 65 ≤ 74; ≥ 75).

Clinical and hematological data are reported in Table 1. Briefly, 52 were male and 61 female, median age was 71 (range 65-92). Stage IA, IIA and IIIA patients numbered 28, 33, 45, respectively, and 7 patients had stage IIIB disease. The M component was IgG in 73 patients (65%), IgA in 30 (26%), IgD in 3 (3%), light chain in 5 (4%). No monoclonal component was detected in serum or urine samples in 2 (2%) cases. Two of the 5 light chain myeloma patients presented impaired renal function at diagnosis. Sixty-three patients had lytic bone lesions that were almost always symptomatic. The presentation features did not differ significantly in patients above or below 75 years of age. Patients were treated according to the policy of each hematological institution participating in this study (see Table 2). First-line treatment was the classical melphalan/prednisone in 84 patients (74%); 29 (26%) patients were treated with other therapies: 12 VMCP (vincristine, melphalan, cyclophosphamide, prednisone), 7 peptichemio, 4 VCAP (vincristine, cyclophosphamide, adriamycin, prednisone), 5 VAD/VND (vincristine, adriamycin, dexamethasone/vincristine, mitoxantrone, dexamethasone) or VAD-MP, 1 CTX-DMZ (cyclophosphamide, dexamethasone). Twenty-two patients received α-IFN as maintenance therapy.

First-line therapy was analyzed in terms of tol-

		All	*≥65 <75*	*≥ 75*
Number of patients		113	84	29
Male/female		52 / 61	40/44	11/18
Age:	mean	71 (65-92)		
	median	70		
Stage	I A	28	21 (25%)	7 (24%)
	IIA	33	28 (33%)	5 (17%)
	IIIA	45	32 (40%)	13 (42%)
	IIIB	7	3 (2%)	4 (7%)
MC:	IgG	73	53	20
	IgA	30	22	8
	IgD	3	3	–
	BJ	5	4	1
	NoMC	2	2	–
Hb g/dL	" "	10.8 (4.5-15)	11.3 (4.8-15)	10 (2.6-13)
WBC x 10^9/L	" "	5.8 (2.1-14)	5.9 (2.1-14)	5.4 (2.6-14)
Plt x 10^9/L	" "	206 (20-520)	204 (20-520)	210 (80-390)
ß2 micr. mg/mL	" "	4.3 (106 pat.)	3.8 (1.4-10)	5.3 (1-5.2)
Marrow PC %	" "	50% (10-90)	50 (10-90)	50 (20-80)
Lytic bone lesions		63 (56 %)	50 (60 %)	13 (45 %)

Table 1. Clinical and hematological features.

Table 2. Treatment and toxicity.

		All	≥65 <75	≥ 75
First-line treatment:	MP	84	61	23
	VMCP	12	9	3
	PTC	7	6	1
	VCAP	4	4	–
	VAD/VND	5	4	1
	CTX-DMZ	1	–	1
Mean dose intensity		93%	95%	87%
Number of WHO	1	14	13	1
Toxicity score	2	12	8	4
	3	14	7	7
	4	3	1	2
Infections during first-line therapy		24	15	9
	BPN/bronch.	8	5	3
	Urin. tract inf.	3	1	2
	FUO	5	3	2
	Enteritis	2	2	-
	Sepsis	1	-	1
	Oral candidiasis	2	1	1
	HSV	1	1	-
	HZV	2	2	-

MP = melphalan, prednisone; VMCP = vincristine, melphalan, cyclophosphamide, prednisone; PTC = peptichemio; VCAP = vincristine, cyclophosphamide, adriamycin, prednisone; VAD/VND = vincristine, adriamycin, dexamethasone/vincristine, mitoxantrone, dexamethasone; CTX-DMZ = cyclophosphamide, dexamethasone.

erability (myelotoxicity according to the WHO grading system, dose intensity, infections) and efficacy (response). An objective response (OR) was defined as a reduction of 51% or more of the M-component (without a simultaneous increase in the number and size of lytic bone lesions). A partial response (PR) was defined as a reduction ranging from 25 to 50%. A reduction of less than 25% or a slight increase of the M component was defined as stable disease (SD). Patients with progressive disease (PD) registered larger increases in the M-component. In non secretory myeloma response was evaluated according to the variation in hematologic parameters and marrow plasma cell infiltration.

Survival times were calculated from the start of treatment to May 1995. No patient was lost to follow-up. Statistical analysis was performed with the t-test and Kaplan-Meier survival curves were produced. We considered a two-tailed p value of less than 0.05 to be an indication of statistical significance.

Results

Therapeutic results

All 113 treated patients were evaluable for response. Overall, seventy-eight (69%) showed a sizable reduction in the tumor mass. Objective and partial response was achieved in 57 (50%) and 21 (19%) patients, respectively. By contrast, thirty-five (31%) patients showed stable or progressive disease. Response rate and outcome of the treated patients are reported in Table 3. MP and other strategies produced comparable percentages of response (66% and 76%, respectively). Moreover, response rate was not influenced by age.

Concerning the outcome, patients with stage I-II disease fared significantly better than the stage III ones (median survival: 70 vs 38 months; p = 0.017) (Figure 1). Early stages (I+II) were grouped together since the median survivals were not statistically different (78 and 58 months, respectively; p = 1). IgG and IgA patients showed similar lengths of survival (data not shown). For younger (< 75) and older (≥

Table 3. Patient outcome.

	All	≥65 <75	≥ 75
Evaluated patients	113	84	29
Total n. of responses:			
OR	57 (50%)	45 (54%)	12 (41%)
PR	21 (19%)	13 (15%)	8 (27%)
SD/PD	35 (31%)	26 (31%)	9 (31%)
Responses to MP therapy	56 (66%)	41 (67%)	15 (65%)
Responses to other therapies	22 (76%)	17 (74%)	5 (83%)
Alive/dead	48/65	35/49	13/16
IFN maintenance	22	17	5
Number of further therapies:	1:38		
	2:26		
	>2:15		

OR = objective response, PR = partial response, SD = stable disease, PD = progressive disease.

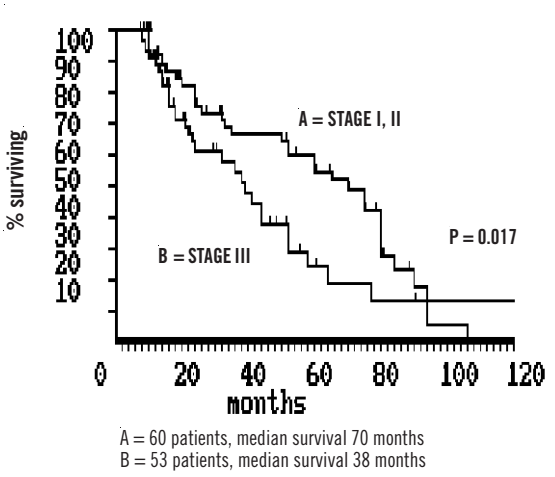

Figure 1. MM in patients over 65 years survival according to stage.

75) patients the response to first-line treatment correlated with overall survival (Figure 2). Patients showing responsive or refractory disease had median survivals of 64 and 20 months respectively (p=0.0001). Patients treated with MP showed longer survival rates than those who received different protocols; however, this may be a misleading result. In fact, since this was not a randomized study, high risk patients preferentially received combination chemotherapy (Tables 4 and 5). The older patients (≥ 75 years of age) showed a trend toward reduced survival (Table 4).

Toxicity

Treatment, which was administered at full dosage, was generally well tolerated, as indicated by the low myelotoxicity score (Table 2), the low number of infective complications and the mean dose intensity reached (93%). There were no significant differences between older and younger patients as far as the type of treatment and myelotoxicity were concerned (Table 2).

When statistical analysis was carried out, 48 patients were still alive and 65 had died. The deaths were directly or indirectly related to MM in 71% of the cases and were caused by concomitant diseases in 29%.

Discussion

In the present study we examined the clinical and laboratory features and the outcome of 113 patients 65 years of age or over treated with conventional therapeutic schemes for symptomatic multiple myeloma.

Although MM is typically a disease of the elderly, considerable efforts to improve the therapeutic results are being made for younger patients. On the other hand, treatment for older

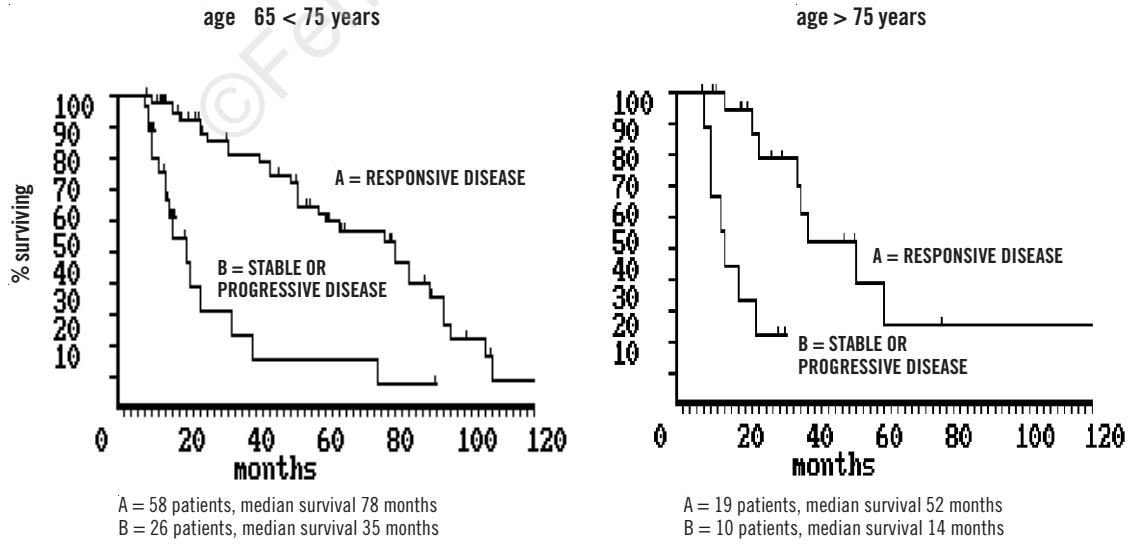

Figure 2. Survival according to response to therapy in MM.

Table 4. Factors influencing survival.

Factor	*Patients*	*Median surv. (months)*	*p.*
Stage I-II	60	70	
Stage III	53	38	0.017
OR or PR	78	64	
SD or PD	35	20	0.0001
MP	84	60	
Other treatments	29	38	0.009
Age ≥ 65 < 75	84	58	
Age ≥ 75	29	36	n.s.

Table 5. Stage, age and therapy.

	All patients		*≥ 65 < 75*		*≥ 75*	
	MP	*other*	*MP*	*other*	*MP*	*other*
stage I	27 (96%)	1 (4%)	20 (95%)	1 (5%)	7 (100%)	–
stage II	26 (79%)	7 (21%)	22 (78%)	6 (22%)	4 (80%)	1 (20%)
stage III	31 (60%)	21(40%)	19 (54%)	16 (46%)	12 (70%)	5 (30%)

MP = melphalan/prednisone; other = other therapies;
It is clear that in the advanced stage the percentage of patients treated with therapies other than MP increases.

patients has not changed in almost 20 years. The general aim of this study was to illustrate what kind of treatment is currently being carried out in this category of patients and to verify whether early diagnosis and improved management of these patients has produced a longer survival rate compared to what had been previously reported.[9-14]

Some of the data collected in this study should be discussed:

a) our series is comparable to those reported in the literature as far as clinical and laboratory features are concerned. Therefore it seems to be a representative sample of the present myeloma population. In patients ≥ 75, stage III is more commonly found than in younger patients (59% vs 42%, respectively). The low number of patients with renal failure at diagnosis is noteworthy. This result may be misleading because many patients who show renal impairment as the first sign of disease are usually seen in nephrology departments and were not included in this series;

b) cyclic melphalan-prednisone was the treatment of choice in the majority of patients, both younger and older and above all with low stage disease, whereas the multidrug combination chemotherapy schemes (VCAP, VMCP and other) were preferentially employed for stage III patients. This reflects the widespread feeling (although not supported by definitive evidence) that a larger tumor mass may benefit from the administration of more intensive and complex sequences of drugs than traditional MP;[13]

c) first-line treatment was well tolerated (as indicated by the low WHO 3-4 grade myelotoxicity and the low number of infections, which were almost always mild) even in patients over 75 years of age. This observation supports the idea that if no major concomitant diseases are present even older patients may be efficiently treated;[26]

d) the observed response rate was in line with that of published series,[8-13] whereas the median survival rate was higher (Figure 3), even in the subset of older patients. Although 47% of the patients had III stage disease, the longer survival rate may be related to the high proportion of median-good prognosis patients in our series, as is also indicated by the low number of patients with impaired renal function at diagnosis, the elevated median values of Hb, platelets and WBC and the relatively low percentage (56%) of patients with lytic bone lesions; however, it should be pointed out that patients with MGUS or smouldering MM were excluded from this study;

e) our data strongly confirm the already established prognostic relevance of tumor mass;[8,25] the median survival rate for stage I-II was significantly higher than that of stage III patients (p = 0.017), both in the overall series and in the two age subgroups.

The prognostic importance of response to first-line therapy for survival has already been debated.[27-30] Our data clearly confirm that patients who obtain at least a partial response to chemotherapy survive longer in both the age

subsets.[30] Reduction of M-component synthesis proved to be a simple and reliable method for evaluating the effect of cytotoxic therapy on the neoplastic burden. Since patients with objective and partial response showed similar lengths of survival, it is suggested that a reduction of the monoclonal component even as low as 25% may exert a positive effect on survival. The type of M-component did not significantly affect the outcome (data not shown).

In this series a slightly higher percentage of responses (though not statistically significant) was obtained with therapies other than MP; however, it is impossible to evaluate the impact on survival. In fact, as was previously pointed out, the composition of the treatment groups was different in term of stage. The younger group, as expected, showed a trend toward longer survival (median survival 60 vs 38 months) and, considering the similar proportion of advanced disease in the two groups, this should be attributed to the increased age-related mortality of the older patients. Similar results were observed by Palva *et al.*,[22] who compared the efficacy of two types of treatment (MP and MOCCA, a five drug combination) in 110 patients aged 70 or over. The response rate was 75% for those treated with MOCCA, which was identical to the rate in younger patients, whereas the response rate achieved with MP was 33% compared to 54% in younger patients. The crude median survivals for patients treated with MP and MOCCA were 39 and 32 months, respectively. In their patients over 70 years of age, the results obtained in the treatment of myeloma were similar to those achieved in younger patients, both in terms of response rate and survival. Not even the *Southeastern Cancer Study Group*[21] observed any significant differences in response rate and outcome between younger and older patients in a large series randomly treated with MP or BCP (carmustine, cyclophosphamide and prednisone). By contrast, Froom and colleagues[23] found that advanced age and low hemoglobin level were the most significant parameters for poor prognosis. In particular, none of their patients over 75 years of age survived longer than 36 months, and 14/17 died within 12 months with a median survival of only 3 months.

α-interferon as maintenance had been given to 22 patients according to the policy of some institutions and not within controlled trials; therefore it was impossible to evaluate the efficacy of IFN in prolonging the length of response.[31] However, these patients showed a survival rate similar to that of responding patients not receiving IFN (data not shown).

In conclusion, our study confirms that older patients with active MM and no severe concomitant disease have outcomes similar to those of younger patients and that response (objective or partial) is significantly related to longer survival, whereas stage III is a negative prognostic factor. These results, due in part to improvements in supportive care and better treatment of complications, suggest that advanced age should not be considered a major obstacle to active treatment, and they also support the option of testing moderately high-dose therapy regimens, even in selected groups of elderly patients with negative prognostic factors or who were refractory to first-line treatment.

References

1. Riedel DA, Pottern LM. The epidemiology of multiple myeloma. Hematol Oncol Clin North Am 1992; 2:225-48.
2. Corradini P, Boccadoro M, Voena C, Pileri A. Evidence for a bone marrow B-cell transcribing malignant plasma cell VDJ joined to Cμ sequence in immunoglobulin (IgG)- and IgA secreting multiple myelomas. J Exp Med 1993; 178:1091-6.
3. Caligaris-Cappio F, Bergui L, Gregoretti MG, Gaidano G, Gaboli M, Schena M. Role of bone marrow stromal cells in the growth of human multiple myeloma. Blood 1991; 77: 2688-93.
4. Carter A, Merchav S, Silvian-Draxler I, Tatarsky I. The role of interleukin-1 and tumour necrosis factor in human multiple myeloma. Br J Haematol 1990; 74:424-31.
5. Bataille R, Jourdan M, Zhang XG, Klein B. Serum levels of interleukin-6, a potent myeloma cell growth factor, as a reflection of disease severity in plasma cell dyscrasias. J Clin Invest 1989; 84:2008-11.
6. Bataille R, Boccadoro M, Klein B, Durie B, Pileri A. C-reactive protein and β2 microglobulin produce a simple and powerful myeloma staging system. Blood 1992; 80:733-7.
7. Greipp PR, Lust JA, O'Fallon MO, et al. Plasma cell labeling index and β2-microglobulin predict survival independently of thymidine kinase and C-reactive protein in multiple myeloma. Blood 1993; 81:3382-7.
8. Gobbi M, Cavo M, Savelli G, Baccarani M, Tura S. Prognostic factors and survival in multiple myeloma. Analysis of 91 cases treated by melphalan and prednisone. Haematologica 1980; 65:437-45.
9. Osterborg A, Ahre A, Bjorkhölm M, et al. Alternating combi-

nation chemotherapy (VMPC/VBAP) is not superior to melphalan/prednisone in the treatment of multiple myeloma patients stage III-A: randomized study from MGCS. Eur J Haematol 1989; 43:54-62.
10. Hjorth M, Hellquist L, Holmberg E, et al. Initial treatment in multiple myeloma: no advantage of multidrug chemotherapy over melphalan-prednisone. Br J Haematol 1990; 74:185-91.
11. Boccadoro M, Marmont F, Tribalto M, et al. Multiple myeloma: VMCP/VBAP alternating combination chemotherapy is not superior to melphalan and prednisolone even in high-risk patients. J Clin Oncol 1991; 9:444-8.
12. Cavagnaro F, Lein JM, Pavlovsky S, et al. Comparison of two combination chemotherapy regimens for multiple myeloma: methyl-CCNU, cyclophosphamide, and prednisone versus melphalan and prednisone. Cancer Treat Rep 1980; 64:73-9.
13. Gregory WM, Richards MA, Malpas JS. Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma: an overview of published trials. J Clin Oncol 1992; 10:334-42.
14. Malpas JS, Bergsagel DE, Kyle RA. Myeloma biology and management. Chapter 11; Oxford Medical Publ., 1995.
15. Gobbi M, Cavo M, Tazzari PL, et al. Autologous bone marrow transplantation with immunotoxin-purged marrow for advanced multiple myeloma. Eur J Haematol 1989; 43(Suppl 51):176-81.
16. Barlogie B, Gharton G. Bone marrow transplantation in multiple myeloma. Bone Marrow Transpl 1991; 7: 71-9.
17. Vesole DH, Barlogie B, Jagannath S, et al. High-dose therapy for refractory multiple myeloma: improved prognosis with better supportive care and double transplants. Blood 1994; 84:950-6.
18. Alexanian R, Dimopoulos MA, Hester J, Delasalle K, Champlin R. Early myeloablative therapy for multiple myeloma. Blood 1994; 84:4278-82.
19. Dimopoulos MA, Hester J, Huh Y, Champlin R, Alexanian R. Intensive chemotherapy with blood progenitor transplantation for primary resistant multiple myeloma. Br J Haematol 1994; 87:730-4.
20. Gahrton G, Tura S, Ljungman P, et al. Allogeneic bone marrow transplantation in multiple myeloma. N Engl J Med 1991; 325:1267-73.
21. Cohen HJ, Bartolucci A. Age and the treatment of multiple myeloma. Southeastern Cancer Study Group Experience. Am J Med 1985; 79:316-26.
22. Palva IP, Ahrenberg P, Ala-Harja K, et al. Treatment of multiple myeloma in old patients. Eur J Haematol 1989; 43:328-31.
23. Froom P, Quitt M, Aghai E. Multiple myeloma in the geriatric patient. Cancer 1990; 66:965-7.
24. Chronic Leukemia-Myeloma Task Force. National Cancer Institute. Proposed guidelines for protocol studies II: plasma cell myeloma. Cancer Chemother Rep 1973; 4:145-58.
25. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975; 36:842-54.
26. Resegotti L. The therapy of hematological malignancies in the elderly. Haematologica 1993; 78:141-4.
27. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol 1983; 1:710-9.
28. Palmer M, Belch A, Brox L, Pollock E, Koch M. Are the current criteria for response useful in the management of multiple myeloma? J Clin Oncol 1987; 5:1373-7.
29. Marmont F, Levis A, Falda M, Resegotti L. Lack of correlation between objective response and death rate in multiple myeloma patients treated with oral melphalan and prednisone. Ann Oncol 1991; 2:191-5.
30. Bladè J, Lopez-Guillermo A, Bosch F, et al. Impact of response to treatment on survival in multiple myeloma: results in a series of 243 patients. Br J Haematol 1994; 88: 117-21.
31. Mandelli F, Avvisati G, Amadori S, et al. Maintenance treatment with recombinant interferon alpha-2 in patients with multiple myeloma responding to conventional induction chemotherapy. N Engl J Med 1990; 322:1430-4.
32. Browman GP, Rubin S, Walker I, et al. Interferon alpha 2b maintenance therapy prolongs progression-free and overall survival in plasma cell myeloma: results of a randomized trial. Proc Am Soc Clin Oncol 1994; 13:408-15.