

Treatment of Multiple Myeloma in Elderly People: Long-term Results in 178 Patients

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Summary

The purposes of the present study have been to analyse the presenting features, response to therapy and survival of myeloma patients aged 70 years or more, in comparison to younger patients. From January 1985 to December 1989, 487 patients with multiple myeloma (MM) were randomized to receive melphalan and prednisone (MP) versus alternating cycles of vincristine, cyclophosphamide, melphalan, and prednisone (VCMP) and vincristine, BCNU, adriamycin, and prednisone (VBAP). The subset of 178 patients who were 70 or more years is the subject of this study, whereas the 309 patients younger than 70 years were used as a control group. The presenting features and response to chemotherapy of older patients were no different to those of the younger population. However, the survival of elderly patients was significantly shorter (median 23.4 vs. 33.5 months, $p < 0.001$). The overall response rate to MP in older patients was 50% (28% objective plus 22% partial response) compared with 61% (44% objective plus 17% partial response) to combination chemotherapy ($p =$ not significant). Myelosuppression was moderate in both arms, although MP produced a higher degree of thrombocytopenia. There were no significant differences in survival between patients given MP versus VCMP/VBAP (median, 20 vs. 27 months, $p = 0.2$). Response to treatment was associated with a significantly longer survival. Older patients with symptomatic myeloma tolerate chemotherapy and should be offered treatment.

Keywords: Multiple myeloma, Elderly people, Prognosis, Chemotherapy.

Introduction

Multiple myeloma is an age-related malignant plasma cell disorder [1]. Less than 15% of patients are below 50 years old at diagnosis and this disease is very uncommon in patients under 40 years [2]. In most series, the median age of patients at diagnosis is about 65 years. Advanced age has been reported to be a negative prognostic factor in some series [3-8]. However, other studies have shown no effect of age on both response to treatment and survival [9-11].

In the present study, the outcome of 178 multiple myeloma patients 70 years or older, from a multicentre series of 487, has been analysed. The main objectives were: (1) to compare the presenting features, response to therapy, and survival of elderly patients with those of patients under 70 years, (2) to compare the efficacy and toxicity of a combination chemotherapy regimen including six drugs with the combination of melphalan and prednisone, and (3) to evaluate whether response to treatment is associated with longer survival in elderly myeloma patients.

Patients and Methods

Patients and diagnostic criteria: From 1 January 1985, to 31 December 1989, 178 patients with symptomatic multiple myeloma aged 70 or more years were entered into a randomized trial of PETHEMA (Programme for the Study and Treatment of Haematological Malignancies, Spanish Society of Haematology). These patients form part of 487 patients included in a randomized trial published elsewhere [12]. Multiple myeloma was diagnosed following the criteria of the Chronic Leukemia-Myeloma Task Force [13]. Patients were stratified according to Durie and Salmon's staging system [14]. Patients with monoclonal gammopathy of undetermined significance [15] and smouldering myeloma were excluded from the study [16]. There was no age limitation for entering the protocol and the exclusion criteria were: active gastroduodenal ulcer, cardiac arrhythmia or heart failure, or patients considered to be terminally ill.

Treatment: Ninety-one patients were allocated melphalan and prednisone (MP) (melphalan 9 mg/m² and prednisone 60 mg/m² orally from days 1 to 4). Eighty-seven patients were assigned alternating cycles of VCMP (vincristine 1 mg i.v. on day 1, cyclophosphamide 500 mg/m² i.v. on day 1, melphalan 6 mg/m² orally on days 1-4, and prednisone 60 mg/m² orally

or parenterally on days 1–4) and VBAP (vincristine 1 mg i.v., BCNU and adriamycin 30 mg/m² each i.v. on day 1, and prednisone 60 mg/m² orally or parenterally on days 1–4). Cycles were administered at 4-week intervals. Evaluation was made after eight courses of therapy. Responding patients received eight additional cycles. Patients who died within the first 2 months from the initiation of treatment were considered as early deaths.

Criteria of response: Response to therapy was assessed according to the criteria of the Chronic Leukemia–Myeloma Task Force [13]. An objective response was defined as (1) a reduction of 50% or more in the M-component size, (2) improvement in the performance status by at least two grades, (3) a decrease of 50% or more in measured cross-sectional area of plasmacytomas, and (4) no increase in lytic bone lesions and correction of anaemia, hypoalbuminaemia, and hypercalcaemia. Patients fulfilling all the above criteria, but with a decrease in the M-component size of less than 50% were considered as partial responders. When the criteria for objective or partial response were not met, the case was considered as a treatment failure.

Statistical methods: The chi-square test was used to assess the statistical significance of multiple comparisons. Survival times were calculated from the start of treatment. Survival curves were plotted according to the method of Kaplan and Meier [17] and statistically compared by means of the log-rank test [18]. To overcome the bias in favour of responders represented by the time necessary to detect the response when considered as an initial variable, the influence of the response to therapy on survival was assessed by the landmark method [19]. In this study, the landmark was situated at the time of response evaluation (i.e. 8 months after the initiation of treatment).

Results

Pretreatment characteristics: The sex, performance status, renal function, serum calcium, haemoglobin level, serum albumin, platelet count, percentage of bone marrow plasma cells, LDH, serum beta₂-microglobulin level, clinical stage, and M-component type of the 178 older patients were similar to those of the 309 patients aged under 70 years.

Response to therapy and toxicity: The overall response rate (objective plus partial) was almost identical

Table I. Response to therapy in the elderly patients

	Treatment group	
	MP (n = 91)	VCMP/VBAP (n = 87)
<i>Not assessable</i>		
Major protocol violation	5	8
Lost to follow-up	2	5
	3	3
<i>Assessable</i>	86	79
Early death	7 (8%)	8 (9%)
Objective response	24 (28%)*	35 (44%)*
Partial response	19 (22%)*	13 (17%)*
Failure	36 (42%)*	23 (30%)*

*p = NS

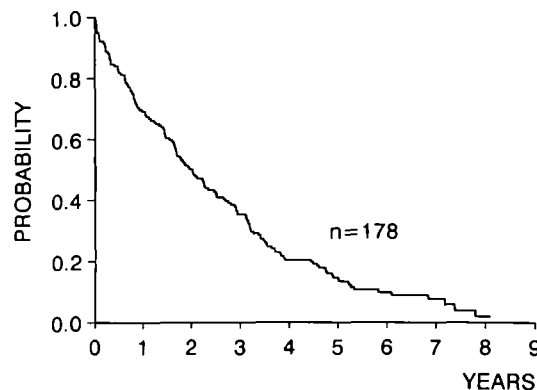


Figure 1. Survival curve from the initiation of treatment of the 178 patients who were 70 or more years old.

between patients younger than 70 years and the older population (57.7% vs. 54.0%, $p = \text{NS}$). In addition, the proportion of early deaths was slightly less than 10% in both age groups and about one third of patients in each group did not respond to the initial chemotherapy. Considering the 178 older patients, 13 could not be evaluated for response for different reasons (Table I). The proportion of early deaths was similar in both treatment groups (8% and 9%). In the 86 evaluable patients treated with MP, the overall response rate was 50% (28% objective plus 22% partial response), while among the 79 patients who were given combination chemotherapy the overall response rate was 61% (44% objective plus 17% partial response) ($p = \text{NS}$).

Treatment was generally administered on an out-patient basis and was clinically well tolerated. During the first eight chemotherapy cycles, the chemotherapy doses were significantly reduced in older patients. Myelosuppression according to treatment arm (World Health Organization scale [20]) in the older population showed no significant differences in WBC and granulocyte counts. In contrast, MP treatment produced a significantly higher proportion of grade 2 or greater thrombocytopenia than alternating VCMP/VBAP chemotherapy (27% vs. 9%, $p = 0.01$).

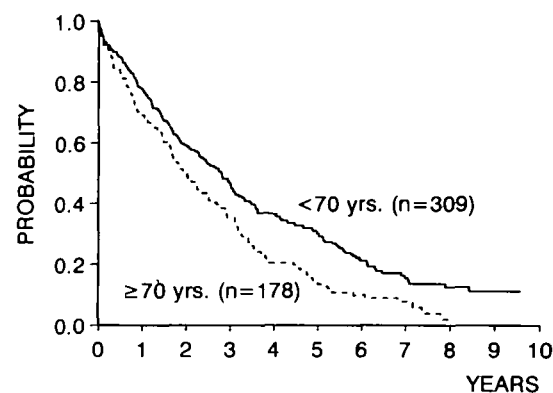


Figure 2. Survival curves from the initiation of treatment of patients aged 70 or more years and patients younger than 70 years ($p < 0.001$).

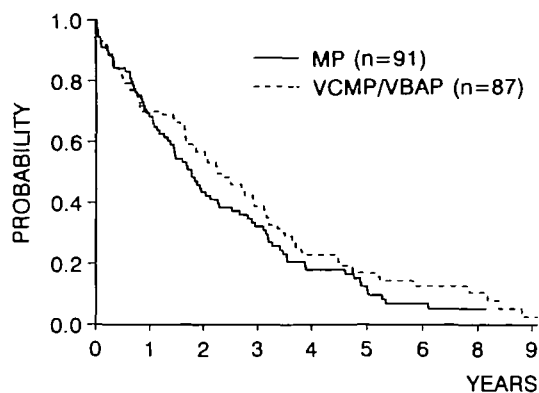


Figure 3. Survival curves from the initiation of therapy of the 178 elderly patients according to treatment arm ($p = NS$).

Survival and causes of death: As of June 1995, 155 of the 178 patients had died. Fourteen (7.9%) patients were lost to follow-up (six within the first year before the response evaluation and eight later during the course of the disease), whereas nine patients (5%) are still alive 65 to 97 months after the initiation of treatment. The median survival for the overall series of older patients is 23.4 months (Figure 1). The survival of the 309 patients younger than 70 years was significantly longer than that of the 178 patients aged 70 years or older (median 33.5 vs. 23.4 months, $p < 0.001$) (Figure 2). There was no statistically significant difference in survival between patients treated with MP and those who received VCMP/VBAP chemotherapy (median 20 vs. 27 months; $p = NS$) (Figure 3). When survival of responders versus non-responders was analysed according to the landmark method (with the landmark at 8 months from the initiation of therapy), a highly significant difference in favour of responders was observed ($\chi^2 = 38.9$, $p < 0.001$) (Figure 4). Disease progression, infection, and renal failure were the main causes of death (Table II). Five patients died from causes other than myeloma or its complications.

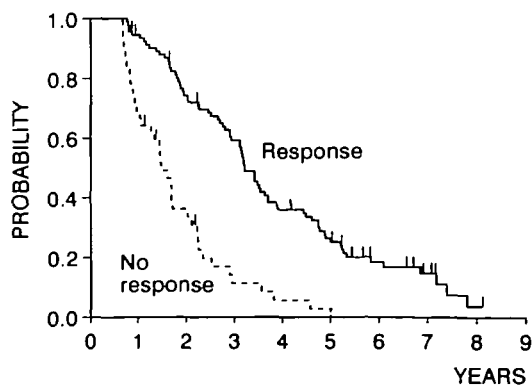


Figure 4. Survival of responders (thick line) versus non-responders (thin line) by the landmark method with the landmark at 8 months after the initiation of therapy ($\chi^2 = 38.9$; $p < 0.001$).

Table II. Causes of death in 155 patients

	n	%
Myeloma progression	53	(34.2)
Infection	42	(27.1)
Renal failure	12	(7.7)
Bleeding	4	(2.6)
Other causes*	6	(3.9)
Unknown	38	(24.5)

* Stroke (three cases), acute myocardial infarction, brain tumour and acute myelogenous leukaemia (one case each).

Discussion

Multiple myeloma is one of the most well established age-related disorders with an increasing incidence with advancing age [1, 21]. Approximately one-third of patients with MM are aged 70 years or more at diagnosis. Despite the frequency of the disease, there is limited information regarding its presenting features and outcome in elderly people. Older people, who accounted for 36% (178/487) of our overall series are well represented in this study. In a large series of patients diagnosed with MM during the last 25 years at one of the participant institutions, the frequency of patients aged 70 years or more was 32% (134/422) [22]. This suggests that our series is representative of elderly myeloma patients.

As in the studies by Cohen and Bartolucci [11] and Fromm *et al.* [3], no significant differences between the presenting features according to age were found in our series. Also, in recent reports from the Nordic Myeloma Study Group (NMSG) [4] and the Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA) [5], no differences in clinical characteristics at diagnosis were observed according to the patient's age.

Response to chemotherapy in patients with MM is about 50–60% [23, 24]. The 54% response rate in our elderly patients is very close to that observed in the general population of patients with MM [23, 24]. This is in agreement with other studies [9–11]. In the present series, the efficacy and toxicity of MP versus VCMP/VBAP have been studied. There was a higher objective response rate with VCMP/VBAP, but the difference did not reach statistical significance, probably owing to the relatively small number of cases. The proportion of early deaths was similar in both groups. Concerning myelotoxicity, MP produced a significantly higher degree of grade 2 to 4 thrombocytopenia than VCMP/VBAP. This was also observed in the general series of 487 patients [12] and may be because in the VCMP/VBAP regimen melphalan is administered at 8-week intervals and at a lower dose than in the MP regimen. In addition, VBAP usually produces moderate myelosuppression, even in patients previously treated with alkylating agents [25, 26].

The median survival of patients with MM ranges

between 2 and 3 years [23, 24]. Although the survival of our elderly patients was significantly shorter than that of younger patients, median survival was still 2 years. These are long-term results, since the analysis was carried out more than 5 years after the last patient entered the study. In contrast, in other studies [9–11] elderly patients had equivalent survival durations to younger patients. The reasons for this discrepancy are unclear. Although the effect of advanced age on the outcome of patients with MM remains controversial [27], the shorter survival of the elderly patients with this disorder should not be surprising and is in agreement with other reports [3–8]. While it is true that some elderly patients with MM die from unrelated disorders, in our series only five patients died from diseases other than myeloma or its complications. As stressed by others [27], this is not expected to have a significant influence in a population with an overall median survival of 2 years.

In two studies no significant correlation between response to treatment and survival was found in patients with MM [28, 29]. However, in a recent single-institution study a significant correlation between response and survival was observed [30]. In the present multicentre series of elderly patients with MM, response to therapy was associated with a significantly longer survival.

In summary, about one-third of patients with MM are aged 70 years or more. The presenting features and response to therapy of these patients are similar to those of the younger population. Melphalan and prednisone is as effective as combination chemotherapy in both response rate and survival and remains the gold standard for MM treatment, particularly in elderly people in whom high-dose therapy is not feasible. Although the survival of older patients is shorter than that of younger subjects, the median survival duration is still 2 years and responding patients survive longer than those failing to respond. Consequently, old patients with clearly symptomatic MM should be actively treated.

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