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Changes in multiple myeloma epidemiology in the last thirty years: A single centre experience

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ABSTRACT

In this study we have evaluated 772 multiple myeloma (MM) patients for clinical presentation, response to treatment, relapse modality, and survival in the last 30 years. Patients were divided, according to the date of diagnosis in group I or group II (before and after 1994, respectively) and therapy (high or conventional dose). Bone pain and early deaths were statistically reduced in group II, whereas MM that evolved from monoclonal gammopathy of undetermined significance (MGUS) had increased. The efficacy of high dose therapy (HDT) over conventional dose therapy (CDT) was confirmed through analysis of response rate, progression free, and overall survival. Relapse modality was similar after HDT or CDT. Among older patients, those diagnosed after 1994 lived longer than those diagnosed before 1994. In the last 30 years, the clinical presentation of multiple myeloma remained substantially unchanged. The new therapeutic approaches, chemotherapy and supportive therapy, allowed better control of the disease with an improvement of survival.

1. Introduction

Multiple myeloma (MM) is an incurable plasma cell neoplasm characterized by heterogeneous clinical presentation. Patients can present with very severe signs and symptoms, such as pathological fractures, anaemia, renal failure or hypercalcemia, or on the contrary, the onset can be insidious and difficult to diagnose [1]. Some authors have investigated if clinical presentation of MM has changed over the years by analysing data from three centre cohorts of patients. The patients were diagnosed in different decades and the authors compared and assessed their clinical presentation. They observed an increasing number of asymptomatic early stage patients in the last decade [2] and ascribed this to improvements in routinely conducted laboratory tests. The clinical characteristics at onset had also changed over the years with a decreased incidence of the most severe complications such as bone disease, hypercalcemia and renal insufficiency [2]. No recent studies have confirmed these data nor assessed the possible changes in MM natural history, due to the use in the last 10–15 years of high dose therapies including autologous transplantation as first-line treatment [3,4]. Many randomised trials have already shown that high-dose therapy guarantees higher response rates, prolonged progression free and overall survival than those reached by conventional treatments. At the same time, atypical patterns of relapse after autologous transplant have been reported with respect to conventional therapy [5], such that in extramedullary

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sites. Improvements in supportive therapies like bisphosphonates [6,7], that are now playing an important role in the control of the bone disease complications, are other variables that have probably contributed to the changing natural history of myeloma. The aims of this study were to evaluate in a single centre population: (1) if the prevalence of different signs and symptoms at MM presentation has changed over the years; (2) if there are any differences in response rate, overall survival (OS) and progression free survival (PFS), modality of relapse, and survival after first relapse (survival after progression [SAP]) between patients who received autologous transplantation and those treated with conventional therapy; and (3) to compare patients aged more than 65 years treated with CDT before or after 1994 to evaluate the impact of supportive care and new salvage therapies on response and survival.

2. Patients and methods

2.1. Patients

Data from 772 consecutive patients diagnosed with MM since 1973 to 31 December 2003 at our institute were collected and computed. Diagnosis and staging were performed according to the criteria by Durie and Salmon and retrospectively applied to 17 patients who were diagnosed before the staging guidelines were published in 1975 [8]. The following clinical and laboratory parameters were gathered: prior diagnosis of MGUS, bone pain, weakness, fever, vertigo or gastrointestinal symptoms; skeletal involvement scored according to the number or radiologically evident lytic lesions (from zero to more than three lesions); type and entity of the monoclonal component (MC); and percentage of bone marrow plasma cells (BMPC). Anaemia was defined as haemoglobin (Hb) value <100 g/l, renal failure as creatinine $\geqslant$2 mg/dl, and hypercalcemia as serum calcium $\geqslant$11 mg/dl. Patients were grouped according to decade of diagnosis (94 patients in 1973–1980, 257 patients in the period 1981–1990, 294 patients since 1991–2000, and 132 patients in the last period 2001–2003). A further analysis was performed for patients diagnosed before 1994 (421 patients) and after 1994 (351 patients), when HDT for patients aged 65 years or less was introduced in the centre.

2.2. Definitions

Study endpoints were defined as follows. Response to first-line therapy was evaluated according to the criteria by Attal [9]. Patients were considered non-responder if response lasted less than 3 months. Early death was considered as death occurring within 4 months from diagnosis. Overall survival was computed from diagnosis to death or last observation for patients still alive. Progression-free survival was computed from the start of first-line therapy to the end of the plateau phase or to the last observation for patients without progression. The observation lasted till 1 March 2003. The following modalities of progression were considered: (1) bone progression – if the main feature at relapse was the occurrence of osteolysis; (2) renal progression – if patients developed clinically evident renal failure; (3) classic progression in presence of an increase of CM or BMPC or both; (4) extramedullary progression when an extraosseous plasmocytoma occurred; and (5) hypercalcemia if serum calcium blood level rose over 11 mg/dl. Survival after progression was computed from the date of progression to the date of death or last observation.

Stage I patients were excluded to reduce spurious heterogeneity, when analyzing response to treatment and progression-free survival. A significant number of stage I patients were treated differently before 1994 from the standard "wait and see" strategy [10–12]. All these endpoints were evaluated in two distinct analyses: for patients aged $\leqslant$65 years and for those $\geqslant$65 years diagnosed before or after 1994.

2.3. Statistical analysis

Continuous variables were reported as median and 25th–75th percentiles, while categorical variables were described as counts and percentages. Patients were compared over periods (<1994 or $\geqslant$1994) and decades by means of Mann–Whitney U test and Kruskall–Wallis test, or by Fisher exact test and χ^2-test for continuous and categorical variables, respectively. Response to HDT or CDT was assessed by means of logistic regression, while controlling for potential confounders (Hb, creatinine, calcium, BMPC levels, skeletal involvement, and stage). For the purpose of the analysis, partial responses, complete response + very good partial response + partial response (CR + VGPR + PR) were compared to the remaining responses. Overall survival, progression-free survival and survival after progression were evaluated in patients aged 65 or less as well as for older patients by means of Kaplan–Meier estimator. Log-rank test was used to compare survival curves. The prognostic role of HDT/CDT on these endpoints, adjusted for confounders, was assessed by Cox regression. The assumption of proportional hazards was verified by means of Schoenfeld residuals.

Stata 8 (StataCorp, College Station, TX) was used for computation; a 2-sided P-value <0.05 was considered statistically significant.

3. Results

3.1. Epidemiology analysis

Table 1 summarises the presentation features of all 772 patients included in our study, overall and according to period (before and after 1994). Table 2 details the distribution of clinical characteristics over decades. The median age of the population at diagnosis was 60 years ranging from 26 to 88 years. No fluctuation was observed over the observation time. Gender was evenly distributed and no variation was observed in time. Almost half of the patients were asymptomatic at diagnosis; among those with symptoms, bone pain was the most frequent, but its incidence reduced after 1994 with a corresponding increase of the other symptoms (P = 0.019 and P = 0.001 for symptoms distributions, according to the 1994 cut-off and over decades, respectively). The most common complication was skeletal involvement: about 50% of patients presented radiological evidence of bone lesions. Its incidence increased from

Table 1 – Features at onset of all 772 patient study population divided according to year of diagnosis: before 1994 (421) and after 1994 (351 subjects)

Clinical characteristics	Overall N (%)	<1994 N (%)	>1994 N (%)	P-value
Gender				0.662
Male	436 (56.5)	235 (55.8)	201 (57.4)	
Female	336 (43.9)	186 (44.2)	150 (42.6)	
Median age (25th–75th)	60 (52–68)	59 (52–67)	60 (53–68)	0.334
Symptoms				0.019
No systemic symptoms	339 (47.1)	187 (47.9)	152 (46.2)	
Bone pain	273 (37.9)	158 (40.5)	115 (34.9)	
Others symptoms	107 (14.9)	45 (11.5)	62 (18.8)	
Stage				0.969
I	272 (37.6)	148 (37.9)	124 (37.2)	
II	115 (15.9)	61 (15.6)	54 (16.2)	
III	336 (46.5)	181 (46.4)	155 (46.5)	
Rx positive	352 (47.7)	181 (43.7)	171 (52.8)	0.017
Haemoglobin (<100 g/l)	223 (32.1)	125 (33.2)	98 (30.8)	0.515
Creatinine ⩾ 2 mg/dl	84 (12.6)	53 (14.5)	31 (10.3)	0.127
Calcium ⩾ 11 mg/dl	69 (8.9)	39 (9.3)	30 (8.5)	0.800
BMPC ⩾ 50 (%)	253 (36.8)	146 (39.9)	107 (33.3)	0.081
Previous MGUS	171 (22.1)	59 (14.0)	112 (31.9)	0.000

Table 2 – Main clinical features of 772 multiple myeloma patients at onset, according to the decade of diagnosis

Year of diagnosis	1973–1980 (%)	1981–1990 (%)	1991–2000 (%)	2001–2003 (%)	P-value
Gender					0.296
Male	48.9	56.4	59.8	54.7	
Female	51.1	43.6	40.2	45.3	
Median age	62	58	61	60	0.190
Symptoms					0.001
No systemic symptoms	56.7	44.6	48.0	43.8	
Bone pain	36.1	44.2	38.2	26.5	
Other symptoms	7.2	11.2	13.8	29.7	
Stage					0.376
I	41.5	35.8	36.2	42.0	
II	20.7	13.3	16.7	16.0	
III	37.8	50.9	47.1	42.0	
Rx positive	37.2	48.6	50.0	48.7	0.184
Haemoglobin < 100 g/l	26.6	36.4	33.5	24.5	0.097
Creatinine ⩾ 2 mg/dl	6.6	16.9	11.5	10.8	0.076
Calcium ⩾ 11 mg/dl	2.1	12.0	6.8	12.6	0.007
BMPC ⩾ 50 (%)	39.5	41.7	35.1	29.6	0.140
Previous MGUS	3.2	15.6	26.9	38.6	0.001

43% before 1994 to 52% after 1994 ($P = 0.017$). The prevalence of renal failure (serum creatinine levels ⩾2 mg/dl) was computed to 12.6%. Anaemia (Hb < 100 g/l) was globally found in 32% of patients. Hypercalcemia occurred in 8.9% of the entire population at diagnosis. Almost one third of the patients had BMPC more than 50%. Patients with a prior history of MGUS were observed more frequently after 1994 (32%) than before (14%) ($P < 0.000$) with an increasing number of diagnoses over the years ($P = 0.001$). The proportion of early deaths was 7.9% before and 2.0% since 1994 (log-rank test $P < 0.001$); it decreased from 9.6% in 1970s, to 9.0% in 1980s, till low incidence in 1990s (1.7%) and 2000s (2.4%) (log-rank test $P < 0.001$).

3.2. *Efficacy of high versus conventional dose therapy*

Patients of group I and II showed comparable clinical characteristics (Table 3), apart from a previous history of MGUS, which was more frequent in HDT patients; and younger age in the HDT group.

The data showed that HDT was more effective than CDT ($P < 0.000$). Table 4 summarises the responses: at least a partial response was obtained in 76 patients in CDT group (43%) and in 85 patients in HDT group (94%) with an adjusted OR = 22.6 (95% CI 8.7–58.4, $P < 0.001$). The good quality responses (CR + VGPR) were obtained in 9 patients (5.1%) in the CDT group and in 60 patients (67%) in the HDT group.

In Fig. 1 the overall survival curves for the HDT and the CDT group are illustrated. One hundred and eighty six patients died (63%) in the CDT group, as compared to 25 (26%) in HDT group; a median OS of 50 months was achieved in CDT patients, which was not reached in HDT group. The death rate more than halved in the HDT group from 14.4 to 6.8 per 100 persons per year, with an adjusted HR = 0.36 (95% CI 0.23–0.56, $P < 0.001$). Similarly the PFS was better for

Table 3 – Main clinical features at onset of patients in stage II/III aged 65 years or less, according to treatment: high-dose therapy (HDT) or conventional-dose therapy (CDT)

Therapy group	CDT 295 pts N (%)	HDT 96 pts N (%)	P-value
Median age (25th–75th)	56 (50–61)	52 (46–57)	0.001
Male	165 (56%)	53 (55%)	0.916
Rx positive	140 (48.3%)	55 (60.4%)	0.054
Haemoglobin < 100 g/l	98 (37.5%)	28 (30.7%)	0.256
Creatinine ⩾ 2 mg/dl	36 (14.6%)	11 (12.3%)	0.722
Calcium ⩾ 11 mg/dl	31 (10.5%)	8 (8.3%)	0.698
BMPC ⩾ 50 (%)	103 (40.5%)	30 (32.2%)	0.172
Precedent MGUS	52 (17.6%)	32 (33.3%)	0.002

Table 4 – Response to first line treatment: conventional dose therapy (CDT) versus high dose therapy (HDT) (P < 0.001)

Response	CDT 177 pts	HDT 90 pts
CR	1 (0.6%)	16 (17.8%)
VGPR	8 (4.5%)	44 (48.9%)
PR	67 (37.8%)	25 (27.8%)
SD	26 (14.7%)	1 (1.1%)
NR	75 (42.4%)	4 (4.4%)

CR, complete remission; VGPR, very good partial response; PR, partial response; SD, stable disease; NR, not responder.

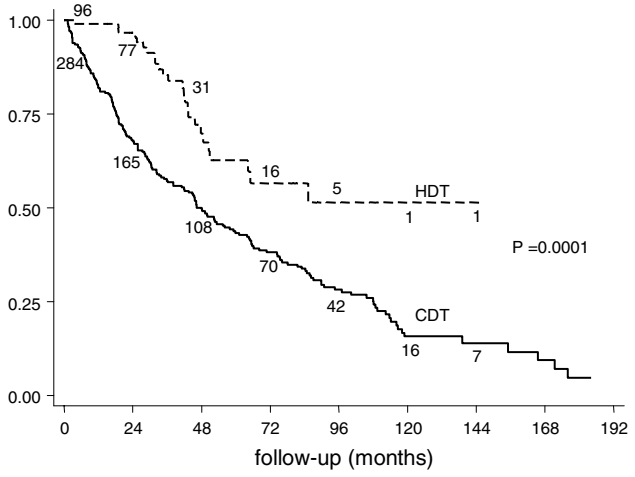

Fig. 1 – Overall Survival of MM patients with age ⩽65 years treated with high-dose therapy (HDT) or with conventional dose therapy (CDT).

the HDT group, with a median of 24 and 37 months for CDT and HDT groups, respectively (Fig. 2). The adjusted HR was computed to 0.46 (0.30–0.70, $P < 0.001$).

3.3. *Modality of relapse after high versus conventional dose therapy*

After HDT, we observed an increased occurrence of extramedullary disease at relapse (12% versus 5%) and a lower occurrence of skeletal involvement (23% versus 35%) with respect to CDT patients with borderline significance ($P = 0.052$). No renal relapse was observed in HDT group with respect to 5% in CDT group; the classic modality of relapse occurred similarly in the two groups (65% in HDT versus 55% in CDT).

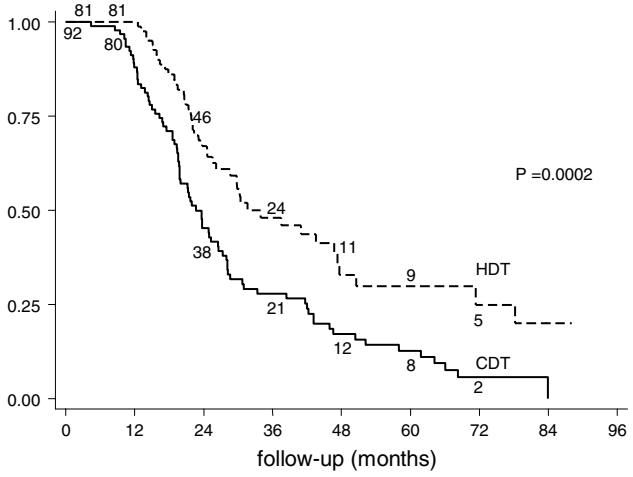

Fig. 2 – Progression-free survival of MM patients with age ⩽65 years treated with high-dose therapy (HDT) or conventional dose therapy (CDT).

3.4. *Survival after progression*

Of the 126 patients who relapsed, 58 (72%) died in the CDT and 23 (50%) in the HDT group. The corresponding median SAP was computed to 18 and 23 months, respectively (Fig. 3), with an adjusted HR = 0.80 (95% CI 0.45–1.42, $P = 0.447$).

3.5. *Elderly population*

The characteristics at presentation for elderly patients were homogeneous – the two groups did not differ in clinical presentation. All patients received conventional dose treatment,

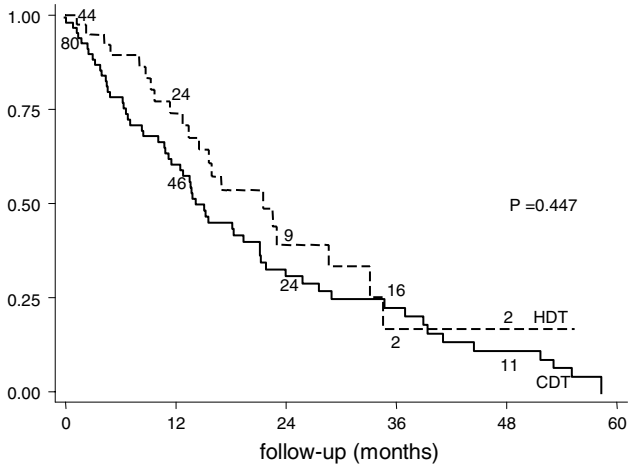

Fig. 3 – Progression-free survival after first progression of MM patients ⩽65 years treated with high-dose therapy (HDT) or conventional-dose therapy (CDT).

but the quality of response improved in recent years with statistical significance ($P = 0.013$). Responsive patients were 33 (51% among valuable patients) after 1994 compared with 28 (32%) before 1994. The good quality responses (CR + VGPR) were achieved in 10 patients (15.4%) after 1994 versus 4 patients (4.5%) before 1994. Also survival data are significantly better after 1994; OS 33 months versus 21 months respectively ($P = 0.01$), PFS 28 months versus 18 months ($P = 0.01$). Survival after progression was not considered due to low numbers of valuable patients (15 and 20 patients in groups I and II, respectively).

4. Discussion

Despite the new treatment options that have been employed in recent years, MM is still an incurable disease with a median survival of about 4–5 years obtained with high-dose therapy [13,14]. Its incidence shows a sharp increase of about 3% per year and the global mortality rate remains stable [15]. This trend was confirmed in Italy by the Eurocare Study showing an increase of new cases of MM between two, five-year periods (1985–1989 and 1990–1994), whereas, relative survival rates were unchanged [16,17]. Sometimes the clinical presentation is dramatic and the quality of life of patients is compromised, particularly because of extensive bone involvement.

We performed this study to evaluate how MM epidemiology has changed in the last thirty years with the introduction of new, more sensitive and reliable laboratory and radiological tests adopted for the diagnosis and the definition of the disease; and high-dose strategies and novel active agents [12,18]. Although this was not a prospective trial, all patients were diagnosed, treated and followed in a single centre. The analysis considered homogeneous groups for clinical features, and to the best of our knowledge, no similar studies have been reported in the literature with these aims.

The median age of our cohort of 772 patients was 60 years, lower than that generally reported in the literature [19,20] and the proportion of younger patients ($\leqslant$50 years) was higher (22%) than that reported [14]. This was probably because high-dose programs are usually performed in the larger reference centres, where younger people are addressed. As reported by Riccardi [2] we also observed in our population, a raising number of myeloma that evolved from MGUS. This confirmed that greater medical attention and higher sensitivity tests had been adopted for clinical practice in the last decade. However, differently from Riccardi, we report a similar percentage of occasional diagnoses of asymptomatic patients before and after 1994, and the distribution of the stages also did not differ between the two periods. In particular, we did not observe more early stages from the past. This result indicates that although better identification of a previous MGUS was observed on the other hand, careful follow-up of high-risk cases was lacking. This was probably due to the exclusive involvement in the follow-up of non-specialised peripheral centres. Alternatively, it is reasonable to conclude that the evolution to overt multiple myeloma is often dramatic and unexpected. Although the radiological evidence of bone lesions was more frequent after 1994, we observed a lower prevalence of bone pain as initial symptom. This is probably due to a more complete assessment of radiological bone evaluation at onset which we systematically applied in our centre since 1990s, resulting in more frequent detection of asymptomatic osteolyses. The prevalence of renal failure (creatinine $\geqslant$2 mg/dl) was 12.6%, less than that reported by most authors [19,21], but in accordance with others [2]. No difference was found before or after 1994 about the prevalence at presentation of renal failure, anaemia, or hypercalcemia. Moreover, in the analysis of presentation features before and after 1994, no difference was found about the type and the entity of monoclonal component. The analysis of early deaths dramatically decreased in the last period, probably due to fast and effective therapies capable of rapidly reducing tumour burden, and to more effective supportive therapies. The same findings were reported by Augustson who studied early mortality in a large myeloma population [22].

It is largely demonstrated that high-dose programs are more effective than conventional-dose therapy in improving survival expectancy of MM [12,13,23]. In patients who underwent intensive treatments, we found impressive remission rates; also the quality of responses was better in HDT group (CR + VGPR: 66.7% versus 5.1%), similarly to that reported by Attal with respect to CDT [13].

The advantage of HDT over CDT is also demonstrated by the longer progression-free and overall survival for patients who underwent autologous transplant. However in our cohort, even patients treated with conventional therapy have durable OS of 50 months which was slightly better than that reported by other authors [12,24]. Median progression-free survival of CDT group was almost 2 years suggesting that if a good response is reached, patients can maintain a long plateau phase. This is supported by other studies [25,26] which underline the importance of obtaining a good response in order to achieve a durable disease control. The real difference is in terms of patient compliance to treatment and percentage of good responses. Patients who enter high-dose programs usually have a period of treatment of variable length after which the therapy is stopped and the patient is followed-up without further treatment. On the other hand, conventional therapies were continued for indefinite periods often until progression, binding the patients to continue difficult long-term programs. Survival after first progression was not statistically different between HDT and CDT. These data are in accordance with other publications [27] and suggest a failure of conventional salvage therapies independently to first-line treatment. Thalidomide has more recently changed the outcome of relapsed patients. However, in our centre it was introduced as salvage strategy after 2000s, so that only a minor portion of patients included in the analysis had this treatment, and this could be the reason for the lack of difference in terms of PFS between the two groups.

As far as the pattern of first relapse was concerned, we also observed as previously reported, a higher incidence of extramedullary relapse after HDT [28–30], but without statistical difference. Skeletal progression was less frequent after HDT, but this could be due to more extensive use of bisphosphonates [31]. Moreover, a more accurate follow-up through biological markers for bone resorption and the application of nuclear magnetic resonance in doubtful cases (negative skeletal rx with high values of bone resorption

parameters) contributed to a precocious diagnosis of bone remodelling before the occurrence of lytic lesions [32]. The absence of renal failure at progression in HDT group of patients is consistent with more accurate monitoring of renal function, usually performed through the assessment of urinary proteins to highlight initial signs of disease progression and anticipating the rising of creatinine serum level [33]. The elderly population of the recent period (group II), surprisingly showed better survival data. The advent of supportive care (growth factors, erythropoetin, bisphosphonates), has probably improved chemotherapy tolerance, and allowed a better and timely therapeutic program that was not always possible in the past. The results of OS and PFS however suggest that, in contrast to younger patients, after first progression older patients did not achieve good control of the disease and death occurred after a short time. Anyway, the number of valuable patients was low in both arms for the analysis of PFS (23 patients before 1994 and 46 patients after 1994), and so these results need to be confirmed by larger studies.

To conclude, this study has shown that: (1) the clinical presentation of myeloma patients did not show substantial modifications from the past, although at present, new and more accurate laboratory and radiological tests are allowing a precocious identification of bone involvement; (2) early deaths are less frequent since effective and prompt therapeutic approaches were adopted; (3) HDT allows higher percentages of good responses and gives longer progression-free and overall survivals; and (4) at the time of first relapse no differences are highlighted between patients treated with CDT or HDT apart from a trend to a minor prevalence of renal failure and skeletal progression.

Conflict of interest statement

None declared.

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