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Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: an analysis of 10 549 patients from the International Myeloma Working Group

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We analyzed the presenting features and survival in 1689 patients with multiple myeloma aged younger than 50 years compared with 8860 patients 50 years of age and older. Of the total 10 549 patients, 7765 received conventional therapy and 2784 received high-dose therapy. Young patients were more frequently male, had more favorable features such as low International Staging System (ISS) and Durie-Salmon stage as well as less frequently adverse prognostic factors including high C-reactive protein (CRP), low hemoglobin, increased serum creatinine, and poor

performance status. Survival was significantly longer in young patients (median, 5.2 years vs 3.7 years; $P < .001$) both after conventional (median, 4.5 years vs 3.3 years; $P < .001$) or high-dose therapy (median, 7.5 years vs 5.7 years; $P = .04$). The 10-year survival rate was 19% after conventional therapy and 43% after high-dose therapy in young patients, and 8% and 29%, respectively, in older patients. Multivariate analysis revealed age as an independent risk factor during conventional therapy, but not after autologous transplantation. A total of 5 of the 10

independent risk factors identified for conventional therapy were also relevant for autologous transplantation. After adjusting for normal mortality, lower ISS stage and other favorable prognostic features seem to account for the significantly longer survival of young patients with multiple myeloma with age remaining a risk factor during conventional therapy. (Blood. 2008;111:4039-4047)

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Introduction

Multiple myeloma is uncommon in young persons. The incidence increases steadily with increasing age to a peak age-specific incidence of more than 40 per 100 000 in persons older than 80 years.^{1,2} Whether the presentation and prognosis of multiple myeloma in young patients differs from the disease usually encountered in the typical elderly patient has only rarely been addressed and never in a large patient cohort. A previous study in 61 patients aged younger than 50 years showed no difference in presenting features compared with older patients.³ Survival was significantly better compared with the older patient cohort but was significantly shorter in young patients after findings were corrected for differences in life expectancy.³ Blade et al reported an increased frequency of renal impairment (30%) and

hypercalcemia (29%) at presentation and median survival of 54 months in 72 patients younger than 40 years.⁴ The question regarding differences in presentation and in outcome in different age groups is clinically relevant since significant differences in prognostic and biologic features have been demonstrated in several other malignancies. Prognosis is significantly better in young patients with acute myeloid leukemia who have less frequently adverse cytogenetic abnormalities,⁵ but significantly worse in young patients with breast cancer whose tumors are less frequently hormone responsive.⁶

Here, we report the presenting features and outcome after conventional and high-dose therapy in 10 549 patients with myeloma and compare the findings obtained in 1689 patients younger than 50 years of age with those of 8860 older patients.

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Methods

A total of 17 institutions and/or study groups from North America, Europe, and Japan participated in this study. A total of 1006 patients were entered from the Japanese myeloma study group, 6457 from European centers (Austria, Spain, France, Italy, Nordic countries, Turkey, and the United Kingdom), and 2386 from North America (Eastern Cooperative Oncology Group [ECOG], National Cancer Institute of Canada [NCIC], Mayo Clinic, Princess Margaret Hospital, Southwest Oncology Group [SWOG], and University of Arkansas for Medical Sciences [UAMS]). Informed consent and approval by the local institutional review board (IRB) were fulfilled as requested at the time of patient enrollment at each participating center. Patients were started on therapy between 1981 and 2002, and part of the information collected was previously used as basis for the generation of the International Staging System (ISS).⁷ Survival status and date of last follow-up were available for 10 750 patients. A total of 23 of those patients were excluded due to unknown age, and 178 were excluded because life tables for their countries were not available, leaving 10 549 patients for inclusion in this analysis. A total of 7765 patients received conventional chemotherapy as first-line treatment, and 2784 patients were subjected to high-dose therapy with planned autologous stem-cell transplantation. The 730 patients who received high-dose treatment as second or later line of therapy were included in the conventional therapy arm. Of the 10 549 patients, 7413 (70%) had been enrolled into clinical trials. The median age of patients enrolled in clinical trials was 60 years, and that of the other patients was 63 years. Median follow-up was 3.25 years (maximum, 19.21 years).

Standard criteria were applied for diagnosis of multiple myeloma.⁸ Patients with smoldering (asymptomatic) myeloma, amyloidosis, and monoclonal IgM-related disorders were not included.

In addition to these cited data, the following information was available: date of start of therapy; sex; ethnicity; race; performance status; hemoglobin level; platelet count; level and type of paraprotein; and serum levels of calcium, creatinine, albumin, LDH, β_2 -microglobulin, and C-reactive protein (CRP). Stage was assessed according to the ISS and the Durie-Salmon system. Furthermore, the percentage of bone marrow plasma cell infiltration and the number of osteolytic lesions was recorded. In 522 patients, conventional cytogenetics was available. Del 13 was assessed by conventional cytogenetics in 454 patients and by fluorescence in situ hybridization (FISH) in 373 patients.

The chi-square test was used to determine significant prognostic factors that distinguish younger from older patients. A maximum likelihood model was used to estimate relative excess risk (RER) for younger versus older patients treated with conventional or high-dose treatment, using a generalized linear model approach with Poisson error structure using exact survival times and collapsed data, as described by Dickman et al.⁹ To determine these estimates, the observed survival was adjusted by dividing by life expectancy depending on age, sex, year of diagnosis, and nationality. Relative survival adjustment was done in order to compare survival between young and old, while taking the normal mortality expectations of respective populations into account. Life tables of estimated population mortality rates for the country of each treating institution were obtained from the Human Mortality Database.¹⁰ Estimates of overall survival within age groups were produced using the Kaplan-Meier method,¹¹ and were compared using the log-rank test.¹² Cox regression analysis¹³ was used to develop a multivariate model of prognostic factors using a stepwise approach considering those factors that were associated univariately with survival with a *P* value of .01 or less. The final model was then adjusted for relative survival to estimate the RER for each prognostic factor.

Results

Median age of all 10 549 patients combined was 60 years. Of these, 1689 (16%) patients were younger than 50 years. Of those, most (1377 [82%] of 1689) were between 40 to younger than 50 years of

age. Only 312 patients were younger than 40 years, and 27 patients were younger than 30 years. Median age of the 8860 patients 50 years or older was 62 years (range, 50-93 years), and the median age of the 1689 patients less than age 50 years was 36 years (range, 20-49 years).

The presenting features of patients younger than 50 years of age versus 50 years and older are shown in Table 1. The younger patients were more frequently ECOG performance status 0 to 1 (64% vs 57%; *P* < .001) and more likely to have ISS stage I (39% vs 26%; *P* < .001), but less often intermediate (stage II: 35% versus 39%; *P* < .001) or advanced ISS stage (stage III: 27% vs 34%; *P* < .001). In addition, young patients presented less often with the adverse prognostic factors low serum albumin (< 35 g/L [< 3.5 g/dL]) and high β_2 -microglobulin (≥ 3.5 mg/dL) serum levels (33% vs 41% and 45% vs 59%; *P* < .001 and *P* < .001, respectively). Likewise, low hemoglobin (< 10 g/dL; 37% versus 41%; *P* = .006), elevated CRP (24% versus 29%; *P* < .007), and increased serum creatinine (≥ 2 mg/dL; 15% vs 17%; *P* < .028) were less common in the patients younger than 50 years. All other prognostically relevant laboratory variables investigated, including serum calcium, LDH, bone marrow plasma cell infiltration, and hematologic variables, did not differ significantly between the 2 groups. Frequency of IgA isotype was slightly lower (21% vs 25%; *P* < .001) and that of light chain myeloma was slightly higher (13% vs 10%; *P* < .002) in the young age cohort.

The group of young patients was further split into a subgroup of very young patients (< 40 years of age) and a subgroup of patients aged 40 to less than 50 years. Table 2 shows a comparison of those parameters, which were found to differ between these age groups. The patients younger than 40 years of age are even more likely to be male (67%), plus have better performance status and lower/better staging.

Median follow-up was 3.25 years (maximum, 19 years) in the entire cohort, 4.09 years (maximum, 19.07 years) in the young patients, and 3.08 years (maximum, 19.21 years) in the patients aged 50 years or older. Relative excess risk of death was significantly higher in older patients (median adjusted for relative survival, 3.7 years vs 5.2 years; RER, 1.26; 95% confidence interval [CI], 1.12-1.42; *P* \leq .001), but did not differ between males and females in the respective groups (median [males vs females], ≥ 50 years, 3.7 years vs 3.7 years; RER, 1.05, 95% CI, 0.996-1.116; *P* = .07; median < 50 years, 5.2 years vs 4.7 years; RER, 0.98, 95% CI, 0.09-1.12; *P* = .81; Figure 1A,B).

Better outcome in the younger cohort was seen in all 3 ISS stages (Figure 1C) and was independent of sex. Better ECOG performance status (≤ 1) was associated with significantly extended survival, both in the younger (median, 5.5 years vs 4.2 years; RER, 0.74; 95% CI, 0.64-0.84; *P* < .001), and in the older cohort (median, 4.2 years vs 2.8 years; RER, 0.67; 95% CI, 0.63-0.71; *P* < .001; Figure 1D). This important interaction between younger age and stage as well as performance status was most obvious in patients treated with conventional therapy (Figure 1Ci,Di), where it was statistically significant versus in those patients treated with high-dose therapy (Figure 1Cii,Dii), for whom it was not statistically significant.

Relative excess risk of death was significantly higher after conventional treatment in the older cohort (median, 3.3 years vs 4.5 years; RER, 1.43; 95% CI, 1.32-1.55; *P* < .001; Figure 2A). This was also reflected by a significantly higher observed 10-year survival rate (19% vs 8%; log-rank *P* < .001) in the younger patients.

Table 1. Patient characteristics, laboratory parameters, and cytogenetic findings in patients younger than 50 years and patients 50 years or older

Factor	Age category		P
	Younger than 50 y, no. (%)	At least 50 y, no. (%)	
Male	1023/1689 (61)	5014/8860 (57)	.002
Performance status 2+	562/1582 (36)	3603/8328 (43)	< .001
ISS			
Stage I	492/1267 (39)	1790/6776 (26)	< .001
Stage II	438/1267 (35)	2675/6776 (39)	< .001
Stage III	337/1267 (27)	2311/6776 (34)	< .001
Durie-Salmon stages I or II	612/1530 (40)	3669/7731 (47)	< .001
Stage I	108/1333 (8)	494/6168 (8)	.910
Stage II	307/1333 (23)	1612/6168 (26)	.019
Stage III	918/1530 (60)	4062/7731 (53)	< .001
Subtype A	1422/1676 (85)	7198/8800 (82)	.003
IgG	924/1538 (60)	4853/8091 (60)	.943
IgA	318/1538 (21)	2009/8091 (25)	< .001
IgD	43/1538 (3)	251/8091 (3)	.522
Light chain only	197/1538 (13)	824/8091 (10)	.002
Measurable M-protein	1091/1340 (81)	6695/7754 (86)	< .001
More than 3 lytic lesions	617/1292 (48)	3457/7423 (47)	.431
No bone lesions	293/1387 (21)	1756/8000 (22)	.492
$\beta 2M \geq 3.5$ mg/dL (≥ 0.2975 μM)	613/1377 (45)	4141/7061 (59)	< .001
Albumin <3.5 g/dL	458/1396 (33)	3276/7912 (41)	< .001
HGB <10 g/dL	596/1614 (37)	3465/8539 (41)	.006
Creatinine ≥ 2 mg/dL (≥ 76.8 μM)	240/1594 (15)	1484/8573 (17)	.028
Platelets <(130 $\times 10^3$) μL	152/1420 (11)	984/8168 (12)	.148
Calcium ≥ 10 mg/dL (≥ 2.5 mM)	481/1445 (33)	2652/7870 (34)	.762
CRP 0.8 mg/dL or more	169/695 (24)	1099/3740 (29)	.007
Bone marrow plasma cells 33% or more	892/1544 (58)	4877/8250 (59)	.325
LDH above normal	158/600 (26)	888/3365 (26)	.977

Where conventional units of measure are given in column 1, SI units follow in parentheses.

High-dose chemotherapy with autologous stem cell transplantation resulted in a higher relative excess risk of death in the older patients (median survival, 5.7 years) compared with the younger patients (median survival, 7.5 years; RER, 1.17; 95% CI, 1.01-1.36; $P = .04$; Figure 2B). Similarly, the observed 10-year survival rate was significantly higher in the younger patients (43% vs 29%; log-rank $P = .005$). Relative survival was similar in the subgroup of patients aged 40 to less than 50 years versus that of very young patients, both after conventional chemotherapy (4.4 years vs 4.7 years; Figure 2C) and after autologous transplantation (7.3 years vs 7.5 years; RER estimates, 1.09 and 0.93, respectively; Figure 2D). The 10-year survival rates were also similar, both after conventional (21% vs 19%; $P = .37$) and after high-dose treatment (44% vs 38%; $P = .76$ by log-rank test).

Conventional therapy was given to 994 (58.9%) of the 1689 patients aged younger than 50 years and to 6771 (76.4%) of the older patients, while high-dose therapy was administered to 695 (41.1%) of the younger patients and to 2089 (23.6%) of the

older patients, respectively. The percentage of young patients enrolled during different time periods for treatment with conventional therapy decreased from 94.2% in the period between 1981 and 1987 to 21.3% in the years between 1999 and 2002 ($P < .001$), while the proportion of those subjected to high-dose therapy increased from 5.7% to 78.7% ($P < .001$; Table 3). The respective figures for older patients were 98.8% to 40.1% ($P < .001$) for conventional therapy, and 1.2% to 59.9% ($P < .001$) for high-dose therapy.

Analysis of patient characteristics by different time periods of enrollment (1981-1986, 1987-1992, 1993-1998, and 1999-2002) revealed a significant improvement of most risk factors over time (Table 4). This effect was almost exclusively seen in patients aged 50 years and older (Table S1, available on the *Blood* website; see the Supplemental Materials link at the top of the online article), while in the younger cohort, no variation of the frequency of poor prognostic features over time of enrollment was observed. Comparison of relative survival between different time periods of enrollment revealed a significant improvement in outcome for patients receiving conventional therapy during the period between 1999 and 2002 (median relative survival not reached vs 3.3 years for the earlier periods; $P < .001$) compared with earlier enrollment periods (Figure 3A). In patients treated with high-dose therapy, relative survival remained constant during the entire period of enrollment (Figure 3B). Both comparisons remain valid even if censoring at 2 or 4 years.

Conventional cytogenetic analysis was available in 522 patients and showed no difference in the frequency of any cytogenetic abnormality (Table 5). Likewise, no significant difference in the proportion of patients with a del 13, determined either by conventional cytogenetics (454 patients) or by FISH (373 patients), was noted in the 2 age cohorts.

Table 2. Clinical and laboratory features, which showed significant different frequencies between the very young (< 40 years old) and the young (40 to < 50 years old) patients

Factor	Age category		P
	Younger than 40 y	40 to younger than 50 y	
Male	208/312 (67)	815/1377 (59)	.015
Performance status 2+	87/296 (29)	475/1286 (37)	.014
ISS stage II	63/219 (29)	375/1048 (36)	.047
Durie-Salmon subtype A	252/310 (81)	1170/1366 (86)	.053
Platelets less than $130 \times 10^9/L$	36/247 (15)	116/1173 (10)	.030

Data are number with factor/number with valid data for factor (%)

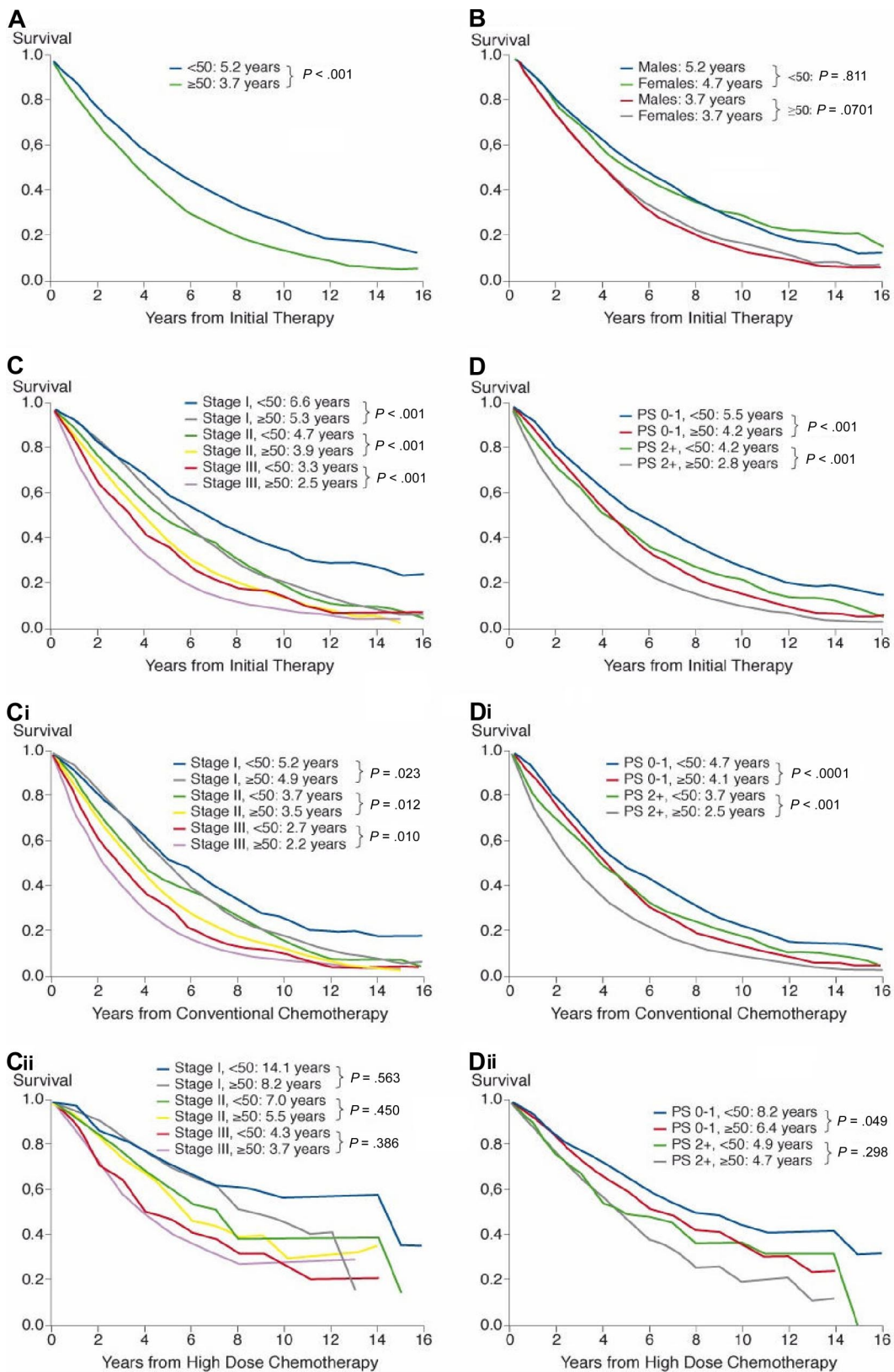


Figure 1. Cumulative relative survival in the entire sample of 10 549 patients stratified by age (A), age and sex (B), age and ISS stage (C), and age and performance status (D) in all patients, in patients treated with conventional therapy stratified by age and stage (Ci) and age and performance status (Di), and in patients treated by high-dose therapy stratified by age and stage (Cii) and age and performance status (Dii). Inserts show median values adjusted for relative survival and P values.

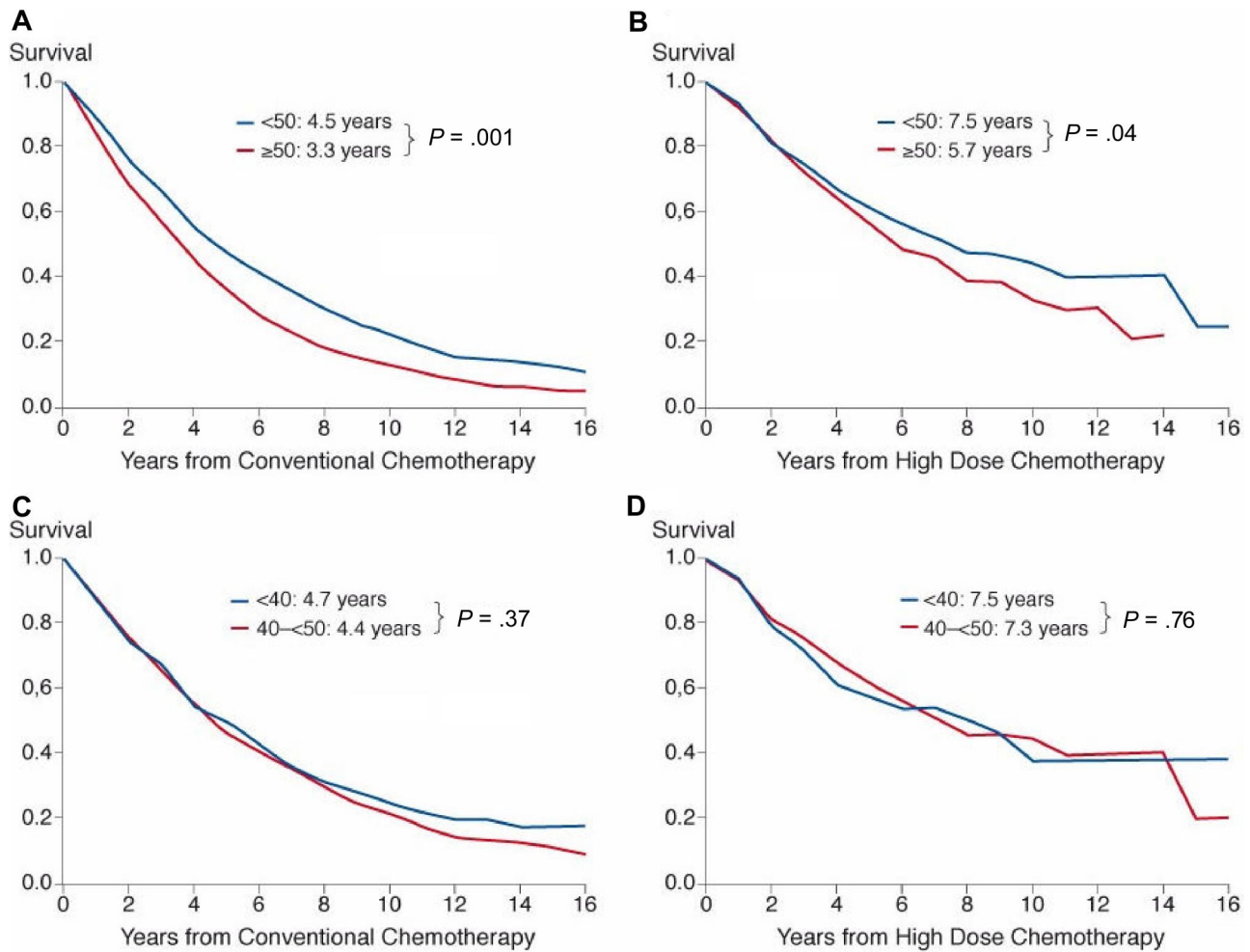


Figure 2. Cumulative relative survival in patients treated with conventional therapy (A) and high-dose therapy (B) in patients younger than 50 years or 50 years and older and in patients younger than 40 years or 40 years and older (C,D). Inserts show median values adjusted for relative survival and P values.

All factors with no more than 15% of values missing (Table 1) were tested in a Cox regression analysis for their prognostic relevance (data not shown). Parameters that in univariate analysis correlated with survival with a significance level of *P* less than or equal to .01 were then considered in a multivariate analysis. Only patients with nonmissing values on all factors were included in the multivariate analysis, reducing the actual number of patients analyzed to 3484 (45%) for those treated with conventional chemotherapy and to 1654 (59%) for those subjected to high-dose therapy. Overall survival between the patients included and those excluded from the multivariate analysis was comparable taking differences by region and time period into account. Of the factors included in multivariate analysis, both higher ISS and Durie-Salmon stage, absence of IgA isotype, higher creatinine (≥ 2 mg/dL) and low

platelet count ($< 130 \times 10^9/L$) were identified as independent risk factors for short survival both in patients treated by conventional or high-dose therapy. In patients started on conventional therapy, older age, performance status, presence of serum M-protein, low hemoglobin (< 10 g/dL), and bone marrow plasma cell infiltration ($\geq 33\%$) were recognized as additional independent prognosticators for poor outcome (Table 6).

Discussion

The most important finding in this study on 10 549 patients with multiple myeloma was the significant differences in the presenting

Table 3. Proportion of patients younger than 50 years old versus older than 50 years old treated with either conventional or high-dose therapy during different time periods

Treatment	Time period, no. (%)			
	1981 to 1987	1988 to 1992	1993 to 1998	1999 to 2002
Younger than 50 y				
Conventional therapy	197 (94.2)	455 (83.9)	299 (40.6)	43 (21.3)
High-dose therapy	12 (5.7)	87 (16.1)	437 (59.4)	159 (78.7)
50 y or older				
Conventional therapy	1.107 (98.8)	3.223 (97.4)	2.003 (60.0)	438 (40.1)
High-dose therapy	13 (1.2)	86 (2.6)	1.336 (36.4)	654 (59.9)

*Chi-square test for equal proportions; all *P* values were less than .001.

Table 4. Change of patient characteristics by time period of enrollment

Factor	Cohort, no. with factor/no. with valid data for factor (%)				P
	1981 to 1987	1988 to 1992	1993 to 1998	1999 to 2002	
Male	642/1120 (57)	1855/3309 (56)	1898/3339 (57%)	619/1092 (57%)	.870
Performance status 2+	532/1093 (49)	1389/3229 (43)	1274/2959 (43%)	408/1047 (39%)	< .001
ISS					
Stage I	131/718 (18)	639/2622 (24)	794/2607 (30)	226/829 (27)	< .001
Stage II	270/718 (38)	1056/2622 (40)	1004/2607 (39)	345/829 (42)	.225
Stage III	317/718 (44)	927/2622 (35)	809/2607 (31)	258/829 (31)	< .001
Durie-Salmon stages I or II	418/961 (43)	1546/3052 (51)	1278/2719 (47)	427/999 (43)	< .001
Stage I	31/657 (5)	195/2306 (8)	182/2273 (8)	86/932 (9)	.007
Stage II	83/657 (13)	605/2306 (26)	650/2273 (29)	274/932 (29)	< .001
Stage III	543/961 (57)	1506/3052 (49)	1441/2719 (53)	572/999 (57)	< .001
Subtype A	835/1117 (75)	2671/3301 (81)	2790/3310 (84)	902/1072 (84)	< .001
IgG	559/1011 (55)	1864/2969 (63)	1799/3091 (58)	631/1020 (62)	< .001
IgA	231/1011 (23)	742/2969 (25)	797/3091 (26)	239/1020 (23)	.191
IgD	48/1011 (5)	93/2969 (3)	97/3091 (3)	13/1020 (1)	< .001
Light chain only	138/1011 (14)	229/2969 (8)	333/3091 (11)	124/1020 (12)	< .001
Measurable M-protein	894/1029 (87)	2284/2603 (88)	2686/3120 (86)	831/1002 (83)	.002
More than 3 lytic lesions	388/854 (45)	1258/2772 (45)	1354/2834 (48)	457/963 (47)	.264
No bone lesions	200/953 (21)	659/2943 (22)	684/3110 (22)	213/994 (21)	.798
$\beta 2M \geq 3.5$ mg/dL (≥ 0.2975 μM)	515/724 (71)	1674/2636 (64)	1467/2790 (53)	485/911 (53)	< .001
Albumin <3.5 g/dL	488/1084 (45)	1308/3131 (42)	1112/2828 (39)	368/869 (42)	.010
HGB <10 g/dL	410/1093 (38)	1267/3119 (41)	1339/3263 (41)	449/1064 (42)	.127
Creatinine ≥ 2 mg/dL (≥ 176.8 μM)	244/1103 (22)	596/3175 (19)	487/3249 (15)	157/1046 (15)	< .001
Platelets <(130 $\times 10^3$) μL	115/1084 (11)	333/3133 (11)	377/2918 (13)	159/1033 (15)	< .001
Calcium ≥ 10 mg/dL (≥ 2.5 mM)	404/1053 (38)	915/2791 (33)	986/3020 (33)	347/1006 (34)	.004
CRP 0.8 mg/dL or more	7/33 (21)	312/1103 (28)	529/1872 (28)	251/732 (34)	.010
Bone marrow plasma cells 33% or more	665/1032 (64)	1810/3049 (59)	1832/3141 (58)	570/1028 (55)	< .001
LDH above normal	63/195 (32)	182/616 (30)	491/1939 (25)	152/615 (25)	.034

Where conventional units of measure are given in column 1, SI units follow in parentheses.

features between young and older patients. Young patients presented with a significantly lower ISS stage and consequently had less frequently elevation of $\beta 2$ -microglobulin and reduction of low serum albumin levels (Table 1). In addition, significantly fewer younger patients presented with poor performance status, anemia, renal impairment, or increased CRP levels. Older patients, in contrast, had a greater prevalence of less favorable prognostic factors. Hence, both a lower ISS stage at diagnosis and overall better prognostic factors seem to account for the superior survival in young patients treated with high-dose therapy after correction for differences in life expectancies, with age remaining an independent risk factor for patients treated with conventional therapy (Table 6). Another relevant finding of this study is the low proportion of young patients observed in the entire group of patients studied, a phenomenon that had been addressed in some prior studies.^{3,4,14} In our investigation, 16% of the patients were younger than 50 years, 3% were younger than 40 years, and 0.26% were younger than 30 years.

The proportion of young patients treated with high-dose therapy was almost twice as high (41.1%) as that of older patients (23.6%;

$P < .001$), and increased steadily during the period patients were enrolled into the various trials (Table 4). A similar, albeit less pronounced increase was seen for older patients reflecting the change in treatment practice with increasing usage of high-dose therapy also in older patients during recent decades.

Young age was found to be significantly associated with longer survival, both after conventional therapy (median, 4.5 years vs 3.7 years; $P < .001$; Figure 2A) and high-dose therapy (median, 7.5 years vs 5.7 years; $P = .04$; Figure 2B). Similar results with high-dose therapy were recently reported by the Nordic Myeloma Study Group.¹⁵ They observed significantly longer survival after high-dose therapy in patients younger than 60 years compared with those aged 60 to 64 years (66 months vs 50 months; $P < .001$), although response rates were similar in both cohorts. The data were, however, not corrected for differences in general life expectancy between these age groups. Other studies such as the analysis of the data of International Blood and Bone Marrow Registry¹⁶ in patients aged younger than 60 years and 60 years and older, and data from Little Rock¹⁷ in patients aged younger

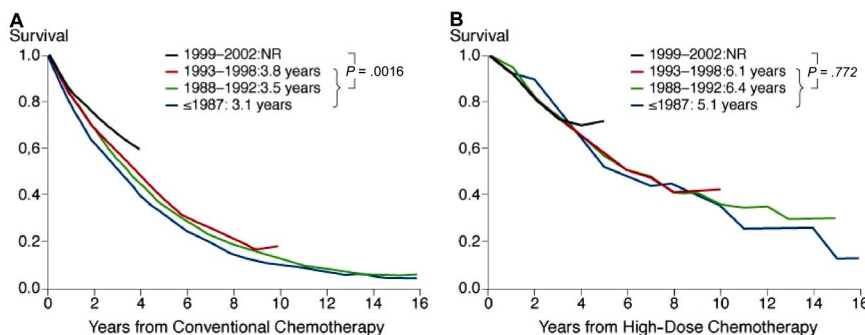


Figure 3. Cumulative relative survival in patients treated during different times of enrollment. (A) Relative survival of conventionally treated patients was significantly longer in those enrolled between 1999 and 2002 compared with patients enrolled earlier ($P < .001$). (B) Relative survival in patients treated with high-dose therapy was similar during the different time periods of enrollment. Inserts show median values adjusted for relative survival and P values.

Table 5. Cytogenetic findings in patients younger than 50 years of age versus those 50 years and older

Factor	Age category, no. with factor/no. with valid data for factor (%)		P
	Younger than 50 y	At least 50 y	
Any clonal CA	30/116 (26)	117/406 (29)	.533
Del13 by cytogenetics	17/109 (16)	45/345 (13)	.499
Del13 by FISH	32/53 (60)	150/320 (47)	.069

CA indicates cytogenetic abnormality.

than 65 years or 65 years and older, in contrast, did not reveal significant differences in survival between younger and older patients. Selection of particularly fit elderly patients and/or shorter follow-up in the latter 2 studies may explain the favorable outcome of these comparisons.

Another interesting finding is the high 10-year observed survival rate observed in both the younger and older patients (43% vs 29%; log-rank $P = .005$) after high-dose chemotherapy. The 10-year survival rates were also significantly higher in the younger patient cohort (19% vs 8%; $P < .001$) subjected to conventional chemotherapy for first-line treatment. These figures are impressive, given the fact that data collection for this study ended before widespread use of thalidomide and the introduction of bortezomib and lenalidomide.

The proportion of patients with favorable prognostic factors increased during the entire enrollment period from 1982 to 2002, with significantly more patients presenting with lower ISS stage and better performance status in the later enrollment periods (Table 4). This effect was almost exclusively seen in the older patients (Table S1) and might be the main reason for the significant improvement in survival of the patients treated with conventional therapy during the latest enrollment period (1999-2002) compared with those enrolled earlier (1982-1998; Figure 3A). Further, better therapy at relapse, with some patients receiving thalidomide and a few even receiving bortezomib as salvage treatment, greater usage of stem cell transplantation after relapse from conventional therapy, and improved supportive care also might have contributed to the increase in survival. The absence of an increase in almost all

favorable prognostic factors in the younger patients (Table S2) over the various time periods might mainly explain why survival did not improve during the last enrollment phase in patients treated with high-dose therapy (Figure 3B). As follow-up was significantly shorter in the young cohort ($P < .001$), the impact of recent improvements in second-line treatment and supportive care on survival may only become apparent after longer follow-up. A recent population based study from Sweden reported an improvement in 1-year relative survival ratios over 4 calendar periods from 1973 to 2003 in all age groups of patients with multiple myeloma.¹⁸ Information about treatment, however, was not available in individual patients. The 5- and 10-year survival ratios increased only in patients younger than 60 and 70 years. A similar increase in 5- and 10-year relative survival was recently found for the United States analyzing the Surveillance, Epidemiology, and End Results (SEER) database.¹⁹ In accordance with the report from Sweden, improvement in survival was only seen in patients younger than 70 years, with highest gains observed in those younger than 50 years of age.

The similar relative and actual 10-year survival (26% vs 24%; $P \leq .57$ by the log-rank test) in the subgroup of very young patients aged younger than 40 years and in the young patients aged between 40 and less than 50 years is noteworthy (Figure 2C,D) and prompted us to combine both groups for further analysis. Nevertheless, the very young patient group presented with slightly lower frequency of poor ECOG performance status (≥ 2) and ISS stage II (Table 2), but high-dose therapy was given to a similar proportion of patients of the very young and young cohort (41.5% vs 39.4%; chi-squared $P = .49$). Blade et al previously reported a 10-year survival rate of 13% in patients aged younger than 40 years and of 31% in a small series of patients aged younger than 30 years.²⁰

Significantly more young patients were male compared with older patients. The preponderance of multiple myeloma in male patients is well known, but our data are surprising because a male predominance was found in 67% of the very young (younger than 40 years) and in 59% of the patients aged 40 to younger than 50 years compared with 57% in those older than 50 years. Experimental mineral

Table 6. RER for factors that were found to correlate independently with survival in multivariate analysis

Factor	Level	RER	95% CI	P
Conventional therapy				
ISS stage (reference stage I)	Stage II	1.26	1.12-1.41	
ISS stage (reference stage I)	Stage III	1.53	1.34-1.74	< .001
Performance status	2+ vs 0-1	1.31	1.20-1.43	< .001
Durie-Salmon stage	III vs I or II	1.24	1.14-1.36	< .001
Platelets	< $130 \times 10^9/L$ vs $\geq 130 \times 10^9/L$	1.38	1.21-1.56	< .001
Bone marrow plasma cell	$\geq 33\%$ vs < 33%	1.23	1.12-1.34	< .001
Age	50+ y vs < 50 y	1.24	1.08-1.41	.001
Hemoglobin	< 100 vs ≥ 100 g/L	1.14	1.04-1.25	.006
IgA isotype	Present vs absent	1.20	1.06-1.36	< .001
Creatinine	$\geq 176.8 \mu M$ vs < $176.8 \mu M$	1.20	1.36-1.07	.003
Serum M protein	Measurable vs not measurable	0.79	0.68-0.92	.002
High-dose therapy				
ISS stage (reference stage I)	Stage II	1.56	1.23-1.97	
ISS stage (reference stage I)	Stage III	2.00	0.52-2.63	< .001
Platelets	< $130 \times 10^9/L$ vs $> 130 \times 10^9/L$	1.72	1.35-2.21	< .001
Durie-Salmon stage	III vs I or II	1.32	1.08-1.61	.007
IgA isotype	Present vs absent	1.31	1.07-1.60	.008
Creatinine	$\geq 176.8 \mu M$ vs < $176.8 \mu M$	1.38	1.06-1.79	.015
Age*	50+ y vs < 50 y	1.17	0.95-1.43	.122

Patients treated with conventional chemotherapy: n = 3484 with nonmissing values on all factors, 45% of 7765 patients; patients treated with high-dose therapy: n = 1654 patients with nonmissing values for all factors, 59% of 2784 patients.

*Not significant, but included for comparison.

oil-induced plasmocytoma occurs more frequently in male mice and 2-methoxyestradiol, an estrogen deriviate, has been shown to exert antimyeloma activity both in cell lines and in myeloma-bearing mice.²¹ Whether increased androgenic sex hormone levels in young males do account for the preponderance of multiple myeloma in very young male adults, however, remains speculative as yet. Overall survival, however, did not differ between male and female patients, which is in contrast to several other cancers such as chronic myeloid leukemia,²² acute myeloid leukemia,²³ and others that show significantly longer survival in female patients.

The frequency of cytogenetic abnormalities was very similar in the younger-than-50-years cohort and in the older-age cohort (26% vs 29%; $P = .533$). Of note, del 13 was found in 16% by conventional cytogenetics and in 60% by FISH in the young patients, and correspondingly in 13% and 47% in the older patients ($P = .499$ and $P = .069$, respectively; Table 5). This agrees with previous findings obtained in 2 smaller studies that did not reveal any association between cytogenetic aberrations and age in a cohort of 75 patients²⁴ and in another group of 172 patients.²⁵ In the latter study, similar frequencies of chromosomal aberrations have been observed in 3 cohorts of patients with different age definitions (younger than 45 years, 45 to 70 years, and older than 70 years) and in all ISS stages. This is in disagreement with a report that indicated a decreasing frequency of IgH translocations with increasing age.²⁶ In our cohort, other parameters such as LDH and bone marrow plasma cell infiltration, which also reflect characteristics of the biology of the myeloma cell population, were evenly distributed between the 2 age cohorts, indicating an absence of a major difference in the biology of the myeloma clone between young or older patients. A similar conclusion has already previously been proposed in a study that compared survival in patients younger or older than 65 years. Differences in absolute survival between these groups disappeared after correction for differences in life expectancy and calculation of relative survival.²⁷

It is also noteworthy that serum calcium and serum creatinine did not differ between the young and very young patients. Blade et al reported in an analysis of 72 patients with myeloma younger than 40 years a relatively high incidence of hypercalcemia (30%) and renal impairment (creatinine level, $\geq 177 \mu\text{M}$; 29%), which was not seen in our patients. They also observed a high frequency (32%) of light chains as the only paraprotein in their young patients, which agrees to some extent with our findings, which also revealed a higher, but less pronounced prevalence of light chain disease in patients aged 50 years or less (13% vs 10%; $P < .002$). As in our study, other laboratory characteristics were similar to those of the general myeloma population. In spite of the high incidence of initial hypercalcemia in their patients, median overall survival was nevertheless found to be 54 months.⁴

The selection of patients for the current analysis was based upon enrollment into clinical studies, including high-dose therapy; hence, the median age overall is lower than the general population of patients with myeloma, with a median age of 65 to 70 years at presentation.^{28,29} However, a higher median age of the entire population would, if anything, have increased the difference in presenting features, which were noted as an important finding in these various analyses.

Multivariate analysis was conducted in patients with nonmissing values on all factors, reducing the number of patients included in the

analysis to 3484 (45%) for those treated with conventional therapy and to 1654 (59%) subjected to high-dose therapy. As overall survival rates between the patients included and those excluded from the multivariate analysis were comparable after correcting for differences by region and by time period, there seems to be no reason to assume that the patient characteristics were different. In patients treated with conventional chemotherapy, 10 parameters were identified as independent risk factors for shortened survival by multivariate analysis (Table 6). Only 5 of these, namely ISS and Durie-Salmon stage, platelet counts, creatinine, and IgA isotype were also identified as independent risk factors in patients treated with high-dose therapy (Table 6). Hence, high-dose therapy seems to overcome the negative impact of some of the unfavorable prognostic factors, including age. The latter finding may be biased by the mode of patient selection for high-dose therapy, as only older patients deemed to be healthy enough for this procedure actually will undergo transplantation. The favorable prognostic importance of a lower ISS stage is expected and has been confirmed in other studies.³⁰ The finding of an IgA isotype, increased serum creatinine, and low platelet counts has previously been reported as prognostically relevant,^{31,32} but the role of these factors is now firmly established due to the large number of patients included in our study.

In conclusion, patients with myeloma younger than 50 years of age had significantly longer age-adjusted survival both after conventional and high-dose therapy (5.4 and 7.5 years, respectively) in relation to older patients (3.7 and 5.7 years, respectively). Given the fact that thalidomide and other new drugs were not available for most patients, the 10-year survival rate was remarkably high in young patients after conventional (19%) and high-dose therapy (43%). The major factors accounting for this improved outcome of young patients were presentation with a lower ISS stage at diagnosis and other more favorable prognostic features.

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Authorship

Contribution: H.L. and B.G.M.D. submitted, analyzed, and interpreted data and drafted the manuscript. V.B. and J.C. analyzed data and commented on the manuscript. I.T., R.A.K., J.B., R.F., MD, K.S., J.S.M., J.W., J.-L.H., M.B., M.B., A.P., B.B., C.S., M.C., P.R.G., M.A., and P.S. submitted and interpreted data, and commented on the manuscript. D.J. interpreted data and commented on the manuscript.

A complete list of the participating study groups can be found in Document S1, available on the *Blood* website; see the Supplemental Materials link at the top of the online article.

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