

Survival and Years of Life Lost in Different Age Cohorts of Patients With Multiple Myeloma

Heinz Ludwig, Vanessa Bolejack, John Crowley, Joan Bladé, Jesus San Miguel, Robert A. Kyle, S. Vincent Rajkumar, Kazuyuki Shimizu, Ingemar Turesson, Jan Westin, Pieter Sonneveld, Michele Cavo, Mario Boccadoro, Antonio Palumbo, Patrizia Tosi, Jean-Luc Harousseau, Michel Attal, Bart Barlogie, A. Keith Stewart, and Brian Durie

From the First Department of Medicine, Wilhelminenspital, Vienna, Austria; Cancer Research and Biostatistics, Seattle, WA; Division of Hematology, Mayo Clinic, Rochester, MN; Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, Little Rock, AR; Mayo Clinic, Scottsdale, AZ; Southwest Oncology Group, International Myeloma Foundation and Cedars Sinai Comprehensive Cancer Center, Los Angeles, CA; Hematology Department, Institute of Hematology and Oncology, Hospital Clinic Institut d'Investigacions Biomediques August Pi i Sunyer, Barcelona; Servicio de Hematología, Hospital Universitario de Salamanca, Centro de Investigación del Cáncer, Instituto de Biología Molecular y Celular del Cáncer (USAL-CSIC), Salamanca, Spain; Department of Medicine, Nagoya City Midori General Hospital, Nagoya, Japan; Department of Hematology, University Hospital, Malmö; Department of Hematology, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg Sweden; Department of Hematology, Erasmus MC, Rotterdam, the Netherlands; Institute of Hematology and Medical Oncology 'Seragnoli,' University of Bologna, Bologna; Servicio de Hematología, Hospital dell'Università di Torino, Ospedaliere-Universitaria San Giovanni Battista di Torino, Torino, Italy; Division of Hematology, Centre Hospitalier Universitaire Hotel-Dieu, Nantes; and Service d'Hématologie, Hôpital Purpan, Toulouse, France.

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Corresponding author: Heinz Ludwig, MD, Department of Medicine I, Center of Oncology and Hematology, Wilhelminenspital, Montleartstr 37, Vienna, Austria 1160; e-mail: heinz.ludwig@wienkav.at.

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A B S T R A C T

Purpose

To assess the impact of age on outcome and to analyze the projected years of life lost in patients with multiple myeloma.

Patients and Methods

Ten thousand five hundred forty-nine patients were evaluated; 6,996 patients were treated with conventional chemotherapy, and 3,553 patients were treated with high-dose therapy with autologous stem-cell transplantation.

Results

Mean observed and relative overall survival times in the entire cohort were 3.7 and 3.9 years, respectively. Observed survival decreased steadily from 6.4 years in patients younger than age 50 years to 2.5 years in patients \geq age 80 years. A similar decrease was noted for relative survival. Higher age correlated significantly with higher International Staging System (ISS) stage. Relative excess risk of death differed significantly between 10-year age cohorts beginning from age 40 years ($P < .001$ for age 50 to 59 ν age 40 to 49, $P < .001$ for age 60 to 69 ν age 50 to 59, $P < .001$ for age 70 to 79 ν age 60 to 69, and $P = .009$ for age \geq 80 ν 70 to 79). The average years of life lost per patient was 16.8 years in the entire patient cohort and decreased steadily from 36.1 years in patients younger than 40 years old to 4.6 years in patients \geq age 80 years.

Conclusion

Age is associated with higher ISS stage and is an important risk factor for early mortality. Survival declined continuously by each decade from age 50 to age \geq 80 from more than 6 to less than 3 years. The average of years of life lost in patients with myeloma is higher than in many other cancers and amounts to more than 30 years in patients younger than 40 years old but decreases to less than 5 years in patients age 80 years or older.

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INTRODUCTION

Multiple myeloma (MM) accounts for 1.4% of all cancers and for 1.9% of all cancer mortality,¹ and the number of new cases per year is 19,920 in the United States¹ and 28,700 in the European Union.² MM is a disease of the elderly population, with a median age at manifestation of approximately 70 years in the United States³ and 72 years in Europe.⁴ Median survival times are 5 to 7 years in patients treated with high-dose chemotherapy and autologous transplantation and 3 to 4 years in patients treated with conventional chemotherapy.⁵ The majority of patients treated with high-dose therapy and autologous transplantation are younger

than 65 years old, whereas patients treated with conventional therapy are usually older than age 65.

Although survival tends to be longer in younger patients,⁵⁻⁷ accurate data on the outcome in patients of different age categories have not been reported. A further important issue regarding information on the projected years of life lost in patients of different age cohorts at diagnosis has not been systematically addressed so far. Estimation of years of life lost provides a more accurate depiction of premature death by weighing deaths occurring at younger ages more heavily than those occurring in older patients and thus functions as an additional tool for quantifying the burden of MM. Here, we report results obtained in a large group of patients with MM treated either with conventional or high-dose therapy.

PATIENTS AND METHODS

Data from 10,549 patients were submitted from 17 institutions or study groups in North America, Europe, and Japan. Patients were enrolled between 1982 and 2002. Six thousand nine hundred ninety-six patients received conventional chemotherapy as first-line treatment, and 3,553 patients were subjected to high-dose therapy with planned autologous stem cell transplantation. The median age of patients enrolled onto clinical trials was 60 years, and the median age of other patients was 63 years. Median follow-up time was 3.25 years (maximum, 19.21 years). Patient characteristics are listed in Table 1.

The relationship between prognostic factors and age was assessed using Spearman rank correlation coefficient.⁸ A maximum likelihood model was used to estimate relative excess risk (RER) for death in patients in different age cohorts using a generalized linear model approach with Poisson error structure using exact survival times and collapsed data, as described by Dickman et al.⁹ Estimates of relative overall survival within age groups were determined using the Kaplan-Meier method¹⁰ and were compared using the log-rank test,¹¹ while taking the normal mortality expectations of respective popula-

tions adjusted for age, sex, year of diagnosis, and nationality into account. Life-tables of estimated population mortality rates for the country of each treating institution were obtained from the Human Mortality Database.¹² Years of life lost were computed by subtracting the actual survival time of individual patients since diagnosis from the patient's life expectancy at the time of diagnosis based on life-tables from the country of origin. The value of the economic loss as a result of premature deaths was estimated using the willingness-to-pay approach multiplying the years of life lost by a previously published value of a year of life of \$150,000.¹³

RESULTS

Patient characteristics are listed in Table 1. More than half of the patients (57.5%) had been enrolled by European study groups or institutions, and 33.2% came from North American and 9.3% from Asian institutions and trials. The majority of patients (70.3%) had been enrolled onto clinical trials, and 84% were 50 years of age or older. χ^2 tests for differences by regions in clinical trials or age were significant at $P < .001$. The distribution of prognostic factors by age category revealed a significant correlation between higher age and more advanced International Staging System (ISS) stage ($r = 0.13$; 95% CI, 0.11 to 0.16) and between age and the parameters that account for ISS stage, namely β_2 -microglobulin ($r = 0.16$; 95% CI, 0.14 to 0.19) and albumin ($r = -0.11$; 95% CI, -0.13 to -0.09 ; Table 2). Lactate dehydrogenase and bone marrow plasma cell infiltration as factors reflecting the biology of myeloma were evenly distributed between all age categories ($r = -0.03$; 95% CI, -0.06 to 0.00; and $r = 0.00$; 95% CI, -0.02 to 0.02, respectively). Median observed and relative survival times in the entire cohort were 3.7 and 3.9 years, respectively, and did not differ significantly between men and women. The median relative survival time decreased steadily in the different age categories from 5.2 years in patients younger than 50 years old to 4.6 years in patients age 50 to 59 years, 3.6 years in patients age 60 to 69 years, 3.1 years in patients age 70 to 79 years, and 2.6 years in patients age ≥ 80 years (Fig 1A); the corresponding median observed survival times were 6.4, 5.3, 4.3, 3.4, and 2.5 years, respectively (Fig 1B). In patients age 40 to 49, 50 to 59, and 60 to 69 years, median observed survival times were 5.7, 4.7, and 4.0 years, respectively, in patients treated with conventional chemotherapy and 8.0, 6.7, and 6.2 years, respectively, in patients treated with high-dose chemotherapy and autologous stem-cell transplantation (Figs 1C and 1D).

RER of death was similar between patients age less than 40 years and patients age 40 to 49 (RER = 1.034, $P = .692$) but differed significantly between all of the other 10-year age categories, with the younger cohort always showing reduced risk of death (age 50 to 59 ν age 40 to 49: RER = 1.201, $P < .001$; age 60 to 69 ν age 50 to 59: RER = 1.288, $P < .001$; age 60 to 69 ν age 70 to 79: RER = 1.190, $P < .001$; age ≥ 80 ν age 70 to 79: RER = 1.278, $P = .009$; Table 3). Similar findings were obtained when RER was analyzed by age category separately in men, women, and patients treated with standard therapy. In patients with autologous transplantation, RER was significantly increased in the age category of 60 to 69 years versus 50 to 59 years (RER = 1.263, $P = .0058$) but not significantly higher in the age category of 70 to 79 years versus 60 to 69 years (RER = 1.130, $P = .7463$). Increased RER estimates for each age group compared with the adjacent age group indicate a trend toward progressively higher risk of death with increasing age, even after adjustment for expected mortality.

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	No. of Patients (N = 10,549)	%*
Age at start of therapy, years		
Median	60	
Range	20-93	
< 40	312	3.0
40-49	1,377	13.0
50-59	3,221	30.5
60-69	3,603	34.2
70-79	1,744	16.5
≥ 80	292	2.8
Sex		
Male	5,253	49.8
Female	5,296	50.2
M component		
IgG	5,777	60.0
IgA	2,327	24.2
Light chain only	1,021	10.6
IgD	294	3.0
Biclonal	8	0.1
Other	202	2.1
Missing	920	—
ISS stage		
I	2,282	28.4
II	3,113	38.7
III	2,648	32.9
Missing	2,506	—
Geographic region		
Asia†	983	9.3
North America	3,499	33.2
Europe	6,067	57.5
Patients in clinical trials by region		
Asia†	983	100
Europe	4,864	80.2
North America	2,549	72.9
Age ≥ 50 years by region		
Asia†	920	93.6
North America	3,009	86.0
Europe	4,931	81.3

Abbreviations: Ig, immunoglobulin; ISS, International Staging System.
 *Percentages are calculated from nonmissing values.
 †Includes Japan only.

Table 2. Prognostic Factors of Patients According to Age Group

Factor	Age Group												Spearman's Correlation Coefficient	95% CI
	< 40 Years		40-49 Years		50-59 Years		60-69 Years		70-79 Years		≥ 80 Years			
	No. of Patients/Total No.	%	No. of Patients/Total No.	%	No. of Patients/Total No.	%	No. of Patients/Total No.	%	No. of Patients/Total No.	%	No. of Patients/Total No.	%		
B2M ≥ 3.5 μg/mL	106/238	45	507/1,139	45	1,354/2,622	52	1,723/2,882	60	922/1,366	67	142/191	74	0.16	0.14 to 0.19
Albumin < 3.5 g/dL	80/251	32	378/1,145	33	1,044/2,758	38	1,325/3,224	41	757/1,651	46	150/279	54	-0.11	-0.13 to -0.09
HgB < 10 g/dL	114/294	39	482/1,320	37	1,186/3,103	38	1,409/3,459	41	724/1,689	43	146/288	51	-0.08	-0.10 to -0.06
Creatinine ≥ 2 mg/dL	51/287	18	189/1,307	14	502/3,107	16	582/3,480	17	341/1,702	20	59/284	21	0.07	0.05 to 0.09
Platelets < 130 × 10 ³ /μL	36/247	15	116/1,173	10	312/2,832	11	432/3,359	13	199/1,690	12	41/287	14	-0.04	-0.06 to -0.02
Calcium ≥ 10 mg/dL	88/256	34	393/1,189	33	999/2,867	35	1,076/3,201	34	501/1,545	32	76/257	30	-0.02	-0.04 to -0.00
CRP ≥ 0.8 mg/dL	27/117	23	142/578	25	412/1,431	29	444/1,477	30	205/704	29	38/128	30	0.06	0.03 to 0.09
BMPC ≥ 33%	165/279	59	727/1,265	57	1,741/2,984	58	1,990/3,336	60	986/1,652	60	160/278	58	0.00	-0.02 to 0.02
LDH > normal	30/95	32	128/505	25	337/1,307	26	369/1,343	27	156/603	26	26/112	23	-0.03	-0.06 to 0.00
ISS stage													0.13	0.11 to 0.16
I	89/219	41	403/1,048	38	785/2,456	32	709/2,783	25	274/1,350	20	22/187	12		
II	63/219	29	375/1,048	36	929/2,456	38	1,115/2,783	40	549/1,350	41	82/187	44		
III	67/219	31	270/1,048	26	742/2,456	30	959/2,783	34	527/1,350	39	83/187	44		

Abbreviations: B2M, β_2 -microglobulin; HgB, hemoglobin; CRP, C-reactive protein; BMPC, bone marrow plasma cells; LDH, lactate dehydrogenase.

In the entire group of patients, the average years of life lost per patient was 16.8 years. The average of years of life lost was highest in patients younger than age 40 years (36.1 years) and decreased steadily (Fig 1B) in patients age 40 to 49, 50 to 59, 60 to 69, 70 to 79, and ≥ 80 (26.9, 19.9, 13.7, 8.1, and 4.6 years, respectively; Table 4). Similar figures with some variations were observed for men and women (Table 4) and for patients treated with standard or high-dose chemotherapy (Table 5). Average years of life lost in patients treated with conventional therapy seemed to be approximately 2 years greater in the age cohorts between 40 and 59 years but 2 years less in patients ≥ age 70 compared with patients treated with high-dose therapy (Table 5).

For all 10,549 patients included in this analysis, the total number of potential years of life lost amounted to 177,306 years (Table 4). Using a standard value of a year of life for men and women of all ages (ie, \$150,000), the value of life-years lost in a myeloma patient diagnosed at age 50 amounts to \$4,035,000, and the value of life-years lost in the entire study population equals \$26,595,900,000.

DISCUSSION

This study documents the significant age dependency of survival in MM. Mean observed survival was 3.7 years in the entire cohort and 6.3 years in patients age less than 50 years. Mean observed survival decreased steadily and significantly with each age decade to 2.5 years in patients age ≥ 80 years. This correlation is remarkable and probably not a result of an increasingly more aggressive phenotype of the myeloma clone because typical risk factors for a more rapid tumor progression, such as lactate dehydrogenase or bone marrow myeloma cell infiltration, did not vary between patients of different age cohorts. The majority of previous studies were also unable to find significant imbalances of cytogenetic risk factors between older and younger patients,^{14,15} and in a small subgroup of 385 patients enrolled onto this study, no correlations between the proportion cytogenetic risk factors

and age were observed (data not shown). However, we found a remarkable correlation between older age and more advanced ISS stage; 41% of patients younger than 40 years of age presented with ISS stage I, but only 12% of patients age ≥ 80 years presented with ISS stage I. ISS stage is defined by β_2 -microglobulin and albumin, both of which correlated with age, with β_2 -microglobulin being more closely associated. β_2 -Microglobulin is an important constituent of the HLA class I surface molecule,¹⁶ which presents intracellularly processed antigens to CD8⁺ T lymphocytes. β_2 -Microglobulin serum levels have been found to correlate with age,¹⁷ renal function,¹⁸ and survival in a series of diseases such as chronic lymphocytic leukemia,¹⁹ Hodgkin's disease,²⁰ non-Hodgkin's lymphoma,²¹ and chronic myelogenous leukemia.²² Our results show that β_2 -microglobulin levels do not correlate with bone marrow myeloma cell infiltration and thus do not directly reflect the tumor mass. Because higher β_2 -microglobulin levels predict poorer outcome in patients with similar stage and age, increased levels may mirror the host's attempt to overcome an insufficient T-cell response against the tumor. This phenomenon seems to accelerate with increasing age and is likely to contribute to poorer outcome in elderly patients. It may also explain, in part, why overall survival has not been improved in the elderly population of myeloma patients after the introduction of immunostimulatory drugs like thalidomide and lenalidomide.²³

Our study revealed an average of 16.8 years of life lost per patient in the entire cohort of 10,549 myeloma patients enrolled onto this study. This is significantly higher than the 12.5 years reported for all cancers combined²⁴ and greater than previously reported for MM. For 2004, the US National Center of Health Statistics reported an average of 14.0 years of life lost for patients with myeloma, with a median age at diagnosis of 70 years.²⁵ In 2007, the British Columbia Cancer Registry reported an average of 12.7 years of life lost as a result of myeloma, whereas for the East Anglia region in the United Kingdom, an average of 10.3 years of life lost was calculated for patients with MM using data obtained between 1990 and 1994.²⁴ The main

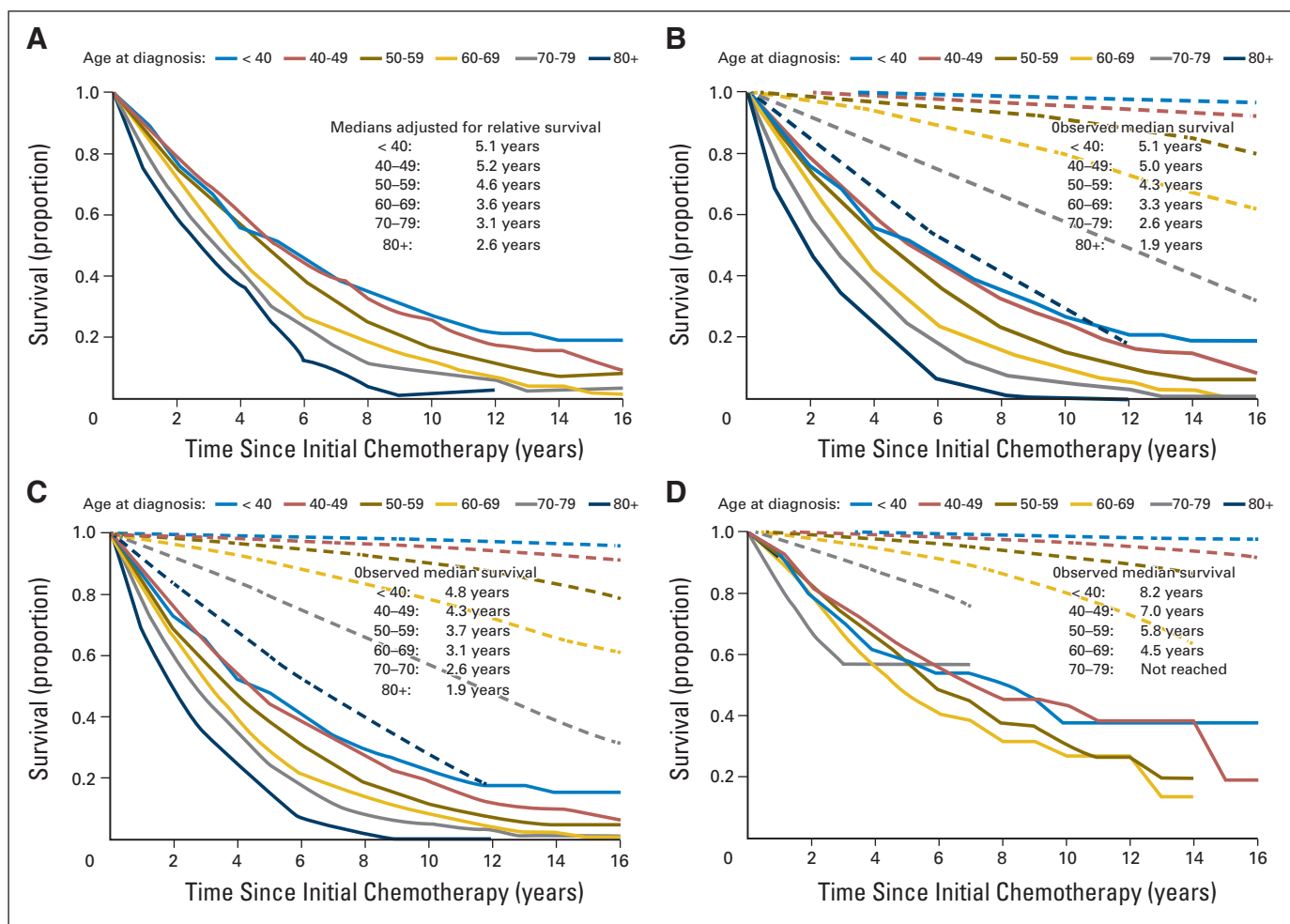


Fig 1. (A) Relative overall survival and (B) observed and expected overall survival in patients according to age at diagnosis. (C) Observed and expected survival in patients treated with conventional chemotherapy according to age at diagnosis. (D) Observed and expected survival in patients treated with high-dose chemotherapy according to age at diagnosis. Solid lines represent observed survival, and dashed lines represent expected survival.

reason for this discrepancy can be ascribed to the lower age of our patients (median age, 60 years), 70% of whom had been enrolled onto clinical studies and 30% of whom were referred for treatment to specialized myeloma centers⁵; in the routine clinical setting, patients are seen at a median age of diagnosis of 70 to 72 years.

This analysis shows the strong dependency of the potential loss of years of life on the age at diagnosis of the disease. The average number of years of life lost decreased more than nine-fold from 36.1 years in patients diagnosed before age 40 years to 4.6 years in patients \geq age 80 years. Another interesting observation is the lesser loss of years of life in the patients age 40 to 49 and 50 to 59 years treated with high-dose chemotherapy and autologous stem-cell transplantation (25.6 and 18.2 years, respectively) compared with conventional therapy (27.4 and 21.0 years, respectively); however, this comparison is limited by the retrospective and nonrandomized nature. Still, this finding corresponds with the notion that the greatest benefit of high-dose therapy and autologous transplantation is derived in patients between 40 and 59 years of age,²⁶ whereas in patients older or younger than this age range, the impact on overall survival of this therapy seems less pronounced.

The total number of estimated years of life lost in our patient cohort is 177,306 years, a figure that is slightly higher than the esti-

mated 151,100 years of life lost for the 10,670 US patients with myeloma who died in the year 2004.³ This higher number is probably a reflection of the younger age of the patients in this analysis.

Some limitations to the present study warrant mention. First, patients analyzed in this study were enrolled over a long period (1982 to 2002). We previously showed that in patients started on conventional therapy, survival increased significantly in patients enrolled between 1998 and 2002 compared with patients entered earlier.⁵ This did not apply to patients treated with high-dose chemotherapy followed by autologous transplantation. Although the improvement in survival in patients enrolled during the last period seems to be partly a result of the introduction of novel drugs, other factors, such as a higher proportion of patients receiving a transplantation at relapse, better supportive care, and a shift in prognostic factors with more patients presenting with more favorable risk factors than previously, may have contributed to the slightly but significantly longer survival.⁵ The longer survival expected with the newly available drugs and the other changes mentioned should markedly reduce the years of life lost of younger patients in the future. Second, forecasting life expectancy by extrapolating from the past does not account for possible new, life-prolonging treatments and may thus underestimate the future gains in survival, limiting the precision of present estimates. Third, there was

Table 3. Relative Excess Risk of Death in Various Patient Subgroups

Subgroup and Age Category	RER	95% CI	P
Age, years			
< 40 v 40-49	1.03	0.88 to 1.22	.692
40-49 v 50-59	1.20	1.10 to 1.31	< .001
50-59 v 60-69	1.29	1.21 to 1.37	< .001
60-69 v 70-79	1.19	1.10 to 1.28	< .001
70-79 v 80+	1.28	1.07 to 1.52	.009
Males			
< 40 v 40-49	1.02	0.84 to 1.26	.818
40-49 v 50-59	1.25	1.11 to 1.40	< .001
50-59 v 60-69	1.30	1.20 to 1.42	< .001
60-69 v 70-79	1.21	1.09 to 1.35	< .001
70-79 v 80+	1.31	0.99 to 1.72	.068
Females			
< 40 v 40-49	1.05	0.79 to 1.38	.757
40-49 v 50-59	1.14	0.99 to 1.31	.051
50-59 v 60-69	1.27	1.15 to 1.41	< .001
60-69 v 70-79	1.18	1.05 to 1.32	.005
70-79 v 80+	1.28	1.02 to 1.61	.046
Conventional chemotherapy			
< 40 v 40-49	1.09	0.90 to 1.32	.359
40-49 v 50-59	1.22	1.11 to 1.35	< .001
50-59 v 60-69	1.16	1.08 to 1.25	< .001
60-69 v 70-79	1.11	1.02 to 1.20	.012
70-79 v 80+	1.27	1.07 to 1.52	.010
High-dose therapy			
< 40 v 40-49	0.93	0.37 to 1.30	.685
40-49 v 50-59	1.10	0.92 to 1.31	.282
50-59 v 60-69	1.26	1.07 to 1.49	.006
60-69 v 70-79	1.13	0.55 to 2.33	.746
70-79 v 80+	—	—	—

Abbreviation: RER, relative excess risk.

significant heterogeneity in the age distribution and inclusion of patients in clinical trials. Patients from Asia were older than those from North America and Europe. All of the Asian patients had been studied within clinical trials, whereas 80.2% of the European and 72.3% of the

North American patients participated in clinical studies. Fourth, the patients included in this analysis, particularly the elderly cohort, were likely in better condition than the general population of myeloma patients that are not entered onto clinical studies because of multimorbidity and/or severe myeloma-related complications such as marked renal impairment or severely suppressed hematopoiesis. Hence, the influence of age might even be greater in a population-based study. Finally, several approaches can be used to estimate the economic burden of mortality. We applied the willingness-to-pay approach that incorporates both lost productivity as a result of death and the intrinsic value of life by estimating the amount an average individual would be willing to pay for an additional year of life.²⁷ We used the commonly used value of \$150,000 for a year of life, which is based on prior research¹³ on the willingness to pay for an additional year of life. Other methods, such as the human capital approach,²⁸ put more emphasis on sex- and age-specific average earnings and combine these values with expected productivity trends and years of life lost to earnings.

Using a standard value of life^{13,29} for men and women of all ages (ie, \$150,000) the value of life lost for our myeloma patients amounts to \$26,595,900,000. Although this figure shows the substantial economic loss of myeloma for the society, the personal loss experienced by the people close to the patient is usually enormous and cannot be measured in financial terms.

In conclusion, age is associated with higher ISS stage and is an important risk factor for early mortality in MM. In addition, survival declines continuously by each decade from age 50 to age ≥ 80 years, even after adjustment for expected mortality. Because of the still relatively short survival of patients with myeloma, the loss in years of life in patients with manifestation before age 40 is greatest and amounts to 36 years, whereas in patients diagnosed at age ≥ 80, the average loss of years of life is approximately 4 to 5 years. Widespread use of the novel drugs thalidomide, bortezomib, and lenalidomide is likely to reduce the loss of precious life time but will not transform myeloma into a chronic disease with a life expectancy similar to that of the healthy population. Better understanding of the underlying process of malignant transformation and tumor propagation ultimately should

Table 4. Mean Years of Expected and Observed Survival and Years of Life Lost for Men and Women

Outcome	Age at Diagnosis						Total	Average
	< 40 Years	40 to 49 Years	50 to 59 Years	60 to 69 Years	70 to 79 Years	≥ 80 Years		
Total patients	312	1,377	3,221	3,603	1,744	292	10,549	
Men	208	562	1,900	1,536	927	120	5,253	
Women	104	815	1,321	2,067	817	172	5,296	
Mean expected survival, years	42.4	33.3	25.2	17.9	11.5	7.1		21.51
Men	40.5	36.3	23.3	20.3	10.2	6.1		21.79
Women	46.1	31.2	28.0	16.2	12.9	7.7		21.25
Mean observed survival, years	6.3	6.4	5.3	4.3	3.4	2.5		4.74
Men	6.0	6.2	5.1	4.1	3.2	2.2		4.56
Women	6.5	6.5	5.4	4.5	3.7	2.6		4.89
Average years of life lost per patient	36.1	26.9	19.9	13.7	8.1	4.6		16.8
Men	34.5	30.1	18.2	16.3	7.0	3.9		17.26
Women	39.7	24.7	22.6	11.6	9.2	5.1		16.33
Potential years of life lost	11,250.9	37,088.4	64,249.8	49,298.4	14,074.9	1,343.6	177,306.0	
Men	7,185.7	16,939.4	34,500.7	24,963.0	6,522.6	464.7	90,576.1	
Women	4,126.1	20,152.1	29,920.2	24,068.9	7,540.4	879.2	86,686.9	

Table 5. Average Years of Life Lost in Patients Treated With Conventional or High-Dose Therapy According to Age Category

Treatment	Age at Diagnosis					
	< 40 Years	40 to 49 Years	50 to 59 Years	60 to 69 Years	70 to 79 Years	≥ 80 Years
Conventional chemotherapy						
No. of patients	123	805	1,259	2,809	1,709	291
Mean expected survival, years	42.7	33.1	25.7	17.6	11.5	7.1
Mean observed survival, years	5.9	5.7	4.7	4.0	3.4	2.5
Average years of life lost per patient	36.8	27.4	21.0	13.6	8.1	4.6
High-dose chemotherapy						
No. of patients	189	572	1,962	794	35	1
Mean expected survival, years	42.2	33.6	25	19.3	12.7	6.1
Mean observed survival, years	6.3	8.0	6.7	6.2	2.1	—
Average years of life lost per patient	35.9	25.6	18.2	13.1	10.6	—

enable the development of more efficient therapy and better outcome of patients afflicted with this still difficult to treat disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Heinz Ludwig, Vanessa Bolejack, John Crowley, S. Vincent Rajkumar, Pieter Sonneveld, Bart Barlogie, Brian Durie **Provision of study materials or patients:** Heinz Ludwig, Joan Bladé, Jesus San Miguel, Kazuyuki Shimizu, Ingemar Turesson, Jan Westin, Pieter Sonneveld, Michele Cavo, Mario Boccadoro, Antonio Palumbo, Patrizia Tosi, Jean-Luc Harousseau, Michel Attal, Bart Barlogie, A. Keith Stewart **Collection and assembly of data:** Vanessa Bolejack, John Crowley, Kazuyuki Shimizu, Ingemar Turesson, Jan Westin, Patrizia Tosi, Bart Barlogie, Brian Durie **Data analysis and interpretation:** Heinz Ludwig, Vanessa Bolejack, John Crowley, Robert A. Kyle, Jan Westin, Pieter Sonneveld **Manuscript writing:** Heinz Ludwig, Vanessa Bolejack, John Crowley, Joan Bladé, Jesus San Miguel, Robert A. Kyle, S. Vincent Rajkumar, Pieter Sonneveld, Antonio Palumbo, Bart Barlogie, Brian Durie **Final approval of manuscript:** Heinz Ludwig, Vanessa Bolejack, John Crowley, Joan Bladé, Jesus San Miguel, Robert A. Kyle, S. Vincent Rajkumar, Kazuyuki Shimizu, Ingemar Turesson, Jan Westin, Pieter Sonneveld, Michele Cavo, Mario Boccadoro, Antonio Palumbo, Patrizia Tosi, Jean-Luc Harousseau, Michel Attal, Bart Barlogie, A. Keith Stewart, Brian Durie

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