EUROPEAN JOURNAL OF CANCER 46 (2010) 160–169

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journal homepage: www.ejconline.com

Improved survival among younger but not among older patients with Multiple Myeloma in the Netherlands, a population-based study since 1989

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ARTICLE INFO

Article history:
Received 20 May 2009
Received in revised form 15 July 2009
Accepted 17 July 2009
Available online 12 August 2009

Keywords:
Plasma-cell myeloma
Trial participation
Survival

ABSTRACT

This study assesses whether new treatment strategies developed in clinical trials translate into improved survival for multiple myeloma (MM) patients in the Netherlands. All patients diagnosed with MM in the Northern part of the Netherlands between 1989 and 2005 were retrieved from two regional population-based cancer registries. Information on study participation was derived from linkage with trial information systems. The effect of period of diagnosis (1989–1992, 1993–1996, 1997–2000, 2001–2005), age (<50, 50–65, 66–74, ⩾75), gender, Salmon–Durie (SD) stage, trial participation and treatment on relative survival were studied. In total 4985 patients were included. When trial participation was analysed for exact periods in which trials were open, 16% of patients aged ⩽65 years with SD-stage I and 38% with SD-stage II or III were enrolled compared to 2% of patients aged >65 years with SD-stage I and 5% with SD-stage II or III. Relative survival decreased with age ($p < .001$), with advanced stage ($p < .001$) and was better for patients enrolled in trials ($p < .001$). Five-year relative survival increased from 34% (95% confidence interval (95% CI) 28–39%) in 1989–1992 to 56% (95% CI 50–61%) in 2001–2005 for patients ⩽65 years. The excess mortality was 37% lower in 2001–2005 than in 1989–1992 for these patients, adjusted for age, stage, trial participation and gender ($p < .001$). Survival did not improve for older patients. In conclusion: MM survival improved among younger but not among older patients since the mid-1990s. The improved survival of younger patients coincided with increasing trial participation and increasing use of high-dose chemotherapy and autologous stem-cell transplantation.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.07.006

1. Introduction

Multiple myeloma (MM), a disease characterised by proliferation and accumulation of monoclonal plasma cells in the bone marrow and overproduction and excretion of monoclonal proteins in serum and urine, is the second most common haematological malignancy in the Netherlands.

The cooperative working party for leukaemia, lymphoma and myeloma in the Netherlands (HOVON) initiates and coordinates clinical trials for haematological malignancies. For MM various trials have been conducted since the mid-1990s. Participating and non-participating hospitals generally consider the standard arm of these trials as the standard treatment for all their patients. Even though only a limited number of patients participate in these trials it is thus still a relevant question whether these trials translate into a survival advantage for the whole Dutch population of MM patients. Furthermore, while the age to standardised incidence of MM has remained rather stable in the Netherlands since 1989, mortality decreased markedly for both males and females (annual percentage change –1.2%, 95% confidence interval (95% CI): –0.6% to –1.8% and –2.1%, 95% CI: –1.5% to –2.7% for males and females, respectively; Fig. 1) which does suggest improving survival.[1]

Until the mid-1990s and for most elderly patients until 2004 the combination of melphalan/prednisone (MP) has been the standard therapy for MM.[2] Since the early 1990s induction chemotherapy, frequently consisting of VAD (vincristin, adriamycin and dexamethason), followed by high-dose melphalan (HDM) and subsequent reinfusion of autologous stem cells (ASCT)[3–9] has been incorporated in the treatment of patients ⩽65 years. During the last few years a number of new treatment modalities have been introduced. Thalidomide, which use was initially based on its anti-angiogenic activity, has been found to improve event free and overall survival when combined with MP.[10,11] This has recently also been shown for the proteasome inhibitor bortezomib in combination with MP.[12] Promising results have been obtained with lenalidomide, a thalidomide analogue, as well.

This population-based study was performed to assess the impact of these recent changes in management of MM on relative survival in the Netherlands and to evaluate determinants of trends in survival.

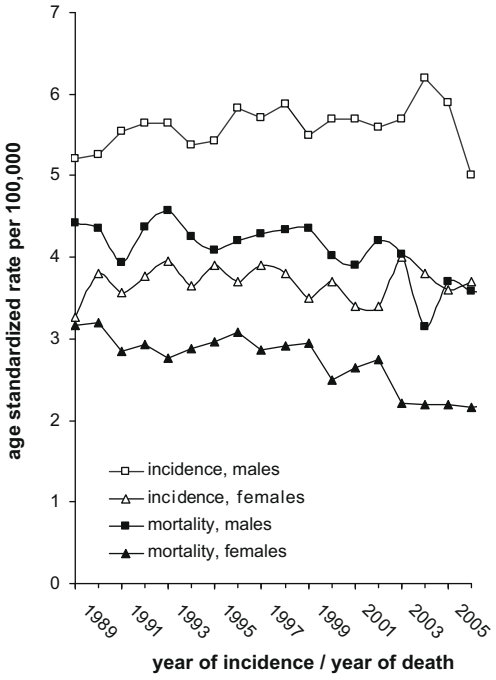

Fig. 1 – Trends in Incidence and mortality of MM in the Netherlands since 1989 by gender.

2. Patients and methods

2.1. Patients

All patients with MM diagnosed in the region of the Comprehensive Cancer Centre North East (CCCNE) and Comprehensive Cancer Centre Amsterdam (CCCA) between January 1989 and January 2006 were eligible for entry in the study. Patients with solitary plasmacytoma and plasma-cell leukaemia and patients with a prior cancer other than non-melanoma skin cancer, within 10 years of the diagnosis of MM, were excluded. The patients were selected from the files of the regional cancer registries, managed by the CCCA and CCCNE, which cover all hospitals in the northern part of the Netherlands, a region with a population of 6.3 million in 2006 (38.6% of the Dutch population). The area is served by 37 community hospitals, three university medical centres, one cancer hospital, nine radiotherapy departments and 20 pathology laboratories.

2.2. Data collection

The cancer registries obtain notifications of new malignancies from PALGA, a Dutch nationwide network and registry of histo- and cytopathology. Notifications are also obtained from haematology laboratories. The national hospital discharge databank, which receives diagnoses of admitted patients from all hospitals, completes case ascertainment. The registries have no access to death certificates. After notification registrars collect data on diagnosis, staging and treatment from the medical records in the hospitals. The data collection occurs at least 6 months after diagnosis allowing comprehensive documenting of all aspects of primary therapy. MM was staged according to the criteria defined by Salmon and Durie (SD)[13] into stage I, II or III regardless of subclass. Only the initial therapy, all treatment started within the first 6–9 months after diagnosis, was recorded. Second-line and salvage treatments were not recorded. Thalidomide use (and more recently bortezomib and lenalidomide) has been recorded since 2004. The cohort was composed in accordance with privacy regulations of the Netherlands Cancer Registries. In the Netherlands the municipal population registries contain information on the vital status of their inhabitants. Since October 1994 population data from all Dutch municipalities are collected in the Dutch municipal base administration. For the period 1989–1994 vital status was established either through linkage of cancer registry data with information from the municipal population registries

within the registry areas, through linkage with the national death registry of the Central Bureau for Genealogy (CBG) or through information derived from the patient's medical records. For the period 1995–2006 vital status was established through linkage with the Dutch municipal base administration. Follow-up ended on 01-02-2008.

2.3. Treatment of multiple myeloma in the Netherlands during the study period

The prevailing treatment during the study period is briefly outlined below. Until 1993 MP was recommended as first-line treatment for all patients treated outside tertiary referral hospitals irrespective of age.[14] Since 1993 increasingly VAD was given to patients ⩽65 years in some cases followed by high-dose cyclophosphamide and stem-cell mobilisation, one EDAP (etoposide, cisplatinum, dexametasone, Ara-C) course or alternative courses of chemotherapy and ASCT.[9] In 1995 the HOVON 24 study was initiated, evaluating the effect of ASCT following VAD induction chemotherapy. Patients were randomised to receive either upfront ASCT or interferon-α maintenance therapy only, although all patients <55 years of age with an HLA-identical donor were candidates for allogeneic stem-cell transplantation.[16,17] This study was followed by the HOVON 50 in 2001, which evaluated the efficacy of thalidomide, adriamycin and dexamethasone (TAD) versus VAD followed by CAD (cyclophosphamide, adriamycin and dexamethasone) and ASCT and maintenance therapy with thalidomide or interferon-α.[18] In 2006 the HOVON 65 trial was initiated comparing VAD with bortezomib, adriamycin and dexamethasone (PAD) followed by CAD and ASCT. Maintenance therapy was thalidomide in the VAD arm and bortezomib in the PAD arm. For patients >65 years MP remained the treatment of choice during the 1990s. The HOVON 36 study, started in 1998 and evaluating melphalan/dexamethasone against MP, was stopped prematurely due to high toxicity levels, especially in the investigational arm. Only 72 patients were registered in this study. In 2002 the HOVON 49 study started, which evaluated MP versus MP and thalidomide. Based on these studies in 2005 the HOVON Myeloma Working Party developed national therapy guidelines, updated in 2007.[19]

2.4. Trial participation

All selected MM patients were linked to the regional Trial Information Systems (TIS) and to its national successor the Trial Registration, Information and Administrative System (TRIAS). These systems are operated by the Comprehensive Cancer Centres and contain information on all patients with MM who are enrolled in regional or national phase II and phase III trials initiated by the HOVON group and the EORTC for which data management is performed by the Comprehensive Cancer Centres.

2.5. Statistics and variable definitions

Analyses were performed for all ages combined and separately for patients up to 66 years of age and patients aged 66 years or over, in accordance with current and past treatment guidelines in the Netherlands. The chi-square test was used to compare distributions of categorical variables. The overall survival was calculated as the time from date of diagnosis until date of death. Otherwise, patients were censored at the date of most recent linkage with the municipal population registries or the date of last contact if lost to follow-up. The expected survival probability was calculated using age, sex and period matched mortality rates from constructed regional life expectancy tables (http://statline.cbs.nl/StatWeb), based on the Ederer II method. The cumulative relative survival, the ratio of the overall and the expected survival, was analysed using Stata (version 10.0) and a relative survival function written by Paul Dickman (www.pauldickman.com). Multivariate analysis of relative survival uses the property that the ratio of two relative survival rates can be considered an excess mortality ratio. Excess mortality rates are calculated by subtracting the expected number from the observed number of deaths and dividing this figure by the accumulated person–years. The excess mortality ratio is given by the ratio of two excess mortality rates. Multivariate excess mortality ratios were estimated in a generalised linear model with a Poisson error structure based on collapsed relative survival data. Using this model the effect of period of diagnosis was studied (1989–1992, 1993–1996, 1997–2000, 2001–2005), while adjusting for the effect of various co-variables on the excess mortality experienced by our cohort. Variables included in the final model were gender, age (<50, 50–65, 66–74, ⩾75 years), SD-stage (stages I, II, III, unknown), trial participation, treatment (including ASCT) and time since diagnosis (1-year intervals).

3. Results

Between 1989 and 2005 4985 patients were diagnosed with MM. The median age at diagnosis was 71 years (inter quartile range 62–79 years) and 33.7% of the patients were ⩽65 years. The age distribution did not change over time for patients ⩽65 nor for older patients. The male patient population was younger (median 70 years) than the female population (median 73 years). Of the female patients 28.1% were ⩽65 years compared to 38.8% of the male patients ($p < 0.001$).

Table 1 shows patient characteristics by age group. Patients ⩽65 years were more often diagnosed at an advanced stage than patients >65 years of age. Furthermore, treatment differed considerably between patients ⩽65 and patients aged >65 years, especially the use of ASCT. Compared to 19.6% of patients aged ⩽65 years only 0.1% of the patients aged >65 years received ASCT. Among patients ⩽65 years, patients aged 18–49 years were more likely to receive ASCT than patients aged 50–65 years (29.6% versus 17.3%, $p = 0.001$). Trial participation was also associated with age. While 20.3% of patients aged ⩽65 years participated in clinical trials only 3.7% of patients aged >65 years did. If the analysis was restricted to the exact periods in which patients could be included in the trials listed in Table 1 (exempting HOVON 16), 32.2% and 7.4% of patients aged ⩽65 and >65 participated, respectively.

Over time the SD-stage distribution changed for all age groups, with predominantly a shift from unknown stage towards stage III and to a lesser extent towards stage II ($p < 0.001$, Table 2). The proportion of stage I patients

Table 1 – Patient and tumour characteristics by patient age.

	All patients		Age ⩽65 years		Age >65 years		*p*-Value
	N	%	*N*	%	*N*	%	
Total	4985	100.0	1679	100.0	3306	100.0	
Gender							*<0.001*
Male	2599	52.1	1008	60.0	1591	48.1	
Female	2386	47.9	671	40.0	1715	51.9	
Age							*n.a.*
Median (IQR)	71 (62–79)		58 (52–63)		76 (71–82)		
18–49	311	6.2	311	18.5	–		
50–65	1368	27.4	1368	81.5	–		
66–74	1457	29.2	–		1457	44.1	
⩾75	1849	37.1	–		1849	55.9	
Period							*0.128*
1989–1992	1062	21.3	349	20.8	713	21.6	
1993–1996	1121	22.5	369	22.0	752	22.8	
1997–2000	1247	25.0	401	23.9	846	25.6	
2001–2005	1555	31.2	560	33.4	995	30.1	
SD-stage							*<0.001*
Stage I	1033	20.7	317	18.9	716	21.7	
Stage II	795	16.0	244	14.5	510	16.7	
Stage III	2439	48.9	924	55.0	1515	45.8	
Unknown	718	14.4	194	11.6	524	15.9	
Treatment							*<0.001*
Chemotherapy (±radiotherapy)	3251	65.2	1038	61.8	2213	66.9	
Chemotherapy and ASCT (±radiotherapy)	331	6.6	329	19.6	2	0.1	
Radiotherapy only	167	3.4	62	3.7	105	3.2	
No therapy/supportive therapy	1236	24.8	250	14.9	986	29.8	
Trial participation							*<0.001*
Yes	462	9.3	340	20.3	122	3.7	
No	4523	90.7	1339	79.7	3184	96.3	
If trial participation, which trial							*n.a.*
HOVON 16 (1991–1997)	54	11.7	22	6.5	32	26.2	
HOVON 24 (1995–2000)	111	24.0	111	32.7	0	0.0	
HOVON 36 (1997–1999)	25	5.4	1	0.3	24	19.7	
HOVON 49 (2002–2007)	70	15.2	4	1.2	66	54.1	
HOVON 50 (2001–2005)	174	37.7	174	51.2	0	0.0	
HOVON 65 (2005–2008)	28	6.1	28	8.2	0	0.0	

decreased slightly over time. As very few trials were available for elderly MM patients (aged >65 years) trial participation was limited during the entire study period: 3.5% during 1993–2000 and 6.1% in the period 2001–2005. Both trial participation and treatment changed over time for patients ⩽65 years ($p < 0.0001$). Whereas 14.6% participated in clinical trials in 1993–1996 this proportion increased to 35.9% in 2001–2005. During the same period the use of ASCT among patients aged ⩽65 years increased from 11.9% to 36.1%. For patients aged 18–49 years the use of ASCT increased from 34.3% in 1993–1996 to 53.5% in 2001–2005, while for patients aged 50–65 years it increased from 6.4% to 32.9%.

Treatment was strongly associated with SD-stage (Table 3). Just over 51% of the stage I patients ⩽65 years and 54% of those aged >65 years did not receive upfront chemotherapy compared to 6% of the patients aged ⩽65 years and 20% aged >65 years with stage III, respectively ($p < 0.001$; Table 3). Trial participation was also associated with SD-stage, as most HOVON protocols excluded patients in stage IA or stage I altogether. Only 12% of the patients ⩽65 years with stage I and 24% of patients with stage II or stage III were enrolled in trials ($p < 0.001$). Fig. 2 shows trial participation by period of diagnosis and SD-stage for both age groups. If trial participation was restricted to the exact periods in which patients could be included in trials, of all patients aged ⩽65 years 15.6% with stage I and 38% with stage II or stage III were enrolled in trials ($p < 0.001$). Only 1.5% of patients aged >65 years with SD-stage I and 5% with SD-stage II or III were enrolled in trials ($p < 0.001$).

3.1. *Relative survival*

Table 4 shows univariate relative survival rates for all patients, for patients aged ⩽65 years and patients aged >65 years at diagnosis. Relative survival did not change over time when all patients were analysed together. However, a clear improvement in 3- and 5-year relative survival was observed for patients aged ⩽65 years (Fig. 3). In this age group the 5-year relative survival increased from 33.8% during 1989–1992 to 55.7% during 2001–2005. Relative survival was

Table 2 – Time trends for stage distribution, trial participation and treatment by age.

	Period									
	1989–1992		1993–1996		1997–2000		2001–2005		Total	
	N	%	N	%	N	%	N	%	N	%
Age ⩽65 years	349	100.0	369	100.0	401	100.0	560	100.0	1679	100.0
SD-stage										
Stage I	74	21.2	68	18.4	84	21.0	91	16.3	317	19.0
Stage II	47	13.5	47	12.7	48	12.0	102	18.2	244	14.4
Stage III	158	45.3	183	49.6	226	56.4	357	63.8	924	55.1
Unknown	70	20.1	71	19.2	43	10.7	10	1.8	194	11.5
Trial participation										
Yes	9	2.6	54	14.6	76	19.0	201	35.9	340	20.3
No	340	97.4	315	85.4	325	81.0	359	64.1	1339	79.7
Treatment										
Chemotherapy[a]	269	77.1	264	71.5	243	60.6	262	46.8	1038	61.8
Chemotherapy and ASCT[a]	1	0.3	44	11.9	85	20.5	202	36.1	329	19.6
No therapy/supportive therapy[b]	79	22.6	61	16.5	76	18.9	96	17.1	312	18.6
Age >65 years	713	100.0	752	100.0	846	100.0	995	100.0	3306	100.0
SD-stage										
Stage I	163	22.9	180	23.9	178	21.0	195	19.6	716	21.7
Stage II	109	15.3	97	12.9	140	16.6	205	20.6	551	16.7
Stage III	256	35.9	338	45.0	405	47.9	516	51.9	1515	45.8
Unknown	185	26.0	137	18.2	123	14.5	79	7.9	524	15.9
Trial participation										
Yes	5	0.7	25	3.3	31	3.7	61	6.1	122	3.7
No	708	99.3	727	96.7	815	96.3	934	93.9	3184	96.3
Treatment										
Chemotherapy[a]	488	68.4	536	71.3	543	64.2	646	64.9	2213	66.9
Chemotherapy and ASCT[a]	0	0.0	0	0.0	1	0.1	1	0.1	2	0.1
No therapy/supportive therapy[b]	225	31.6	216	28.7	302	35.7	348	35.0	1091	33.0
All patients	1062	100.0	1121	100.0	1247	100.0	1555	100.0	4985	100.0
SD-stage										
Stage I	237	22.3	248	22.1	262	21.0	286	18.4	1033	20.7
Stage II	156	14.7	144	12.9	188	15.1	307	19.7	795	16.0
Stage III	414	38.9	521	46.5	631	50.6	873	56.1	2439	48.9
Unknown	255	24.0	208	18.6	166	13.3	89	5.7	718	14.4
Trial participation										
Yes	14	1.3	79	7.1	107	8.6	262	16.9	462	9.3
No	1048	98.7	1042	92.9	1140	91.4	1293	83.1	4523	90.7
Treatment										
Chemotherapy[a]	757	71.3	800	71.4	786	63.0	908	58.4	3251	65.2
Chemotherapy and ASCT[a]	1	0.1	44	3.9	83	6.7	203	13.1	331	6.6
No therapy/supportive therapy[b]	304	28.6	277	24.7	378	30.3	444	28.6	1403	28.1

a With or without radiotherapy.
b Includes radiotherapy only.

not associated with gender but decreased with older age among patients ⩽65 years as well as among patients aged >65 years. Relative survival also decreased with more advanced stage. Trial participation was associated with better relative survival irrespective of age group.

Multivariate analysis also showed a significant decrease in excess mortality for patients ⩽65 years diagnosed in more recent years (Fig. 4). Adjusted for gender, age and stage patients diagnosed during 2001–2005 had 43% lower mortality compared to patients diagnosed during 1989–1992 ($p < 0.001$). Both trial participation and changes in therapy, especially increasing use of chemotherapy followed by ASCT, explained part of the association of later period of diagnosis with relative survival. Adjusted for trial participation and treatment patients diagnosed during 2001–2005 still had a 27% lower mortality compared to patients diagnosed during 1989–1992 ($p = 0.002$, Table 5). Trial participation was associated with a 39% lower excess mortality among patients aged >65 years. Excess mortality did not change with time for patients aged >65 years.

Table 3 – Treatment according to age and Salmon–Durie stage.

	SD-stage							
	Stage I		Stage II		Stage III		Stage unknown	
	N	%	N	%	N	%	N	%
Age ⩽65 years								
Treatment								
Chemotherapy[a]	121	38.2	151	61.9	634	68.6	132	68.0
Chemotherapy and ASCT[a]	33	10.4	54	22.1	232	25.1	10	5.2
No therapy/supportive therapy[b]	163	51.4	39	16.0	58	6.3	52	26.8
Trial participation								
Yes	39	12.3	45	18.4	234	25.3	22	11.3
No	278	87.7	199	81.6	690	74.7	172	88.7
Age >65 years								
Treatment								
Chemotherapy[a]	329	46.0	397	72.1	1211	79.9	276	52.7
Chemotherapy and ASCT[a]	1	0.1	0	0.0	1	0.1	0	0.0
No therapy/supportive therapy[b]	386	53.9	154	27.9	303	20.0	248	47.3
Trial participation								
Yes	11	1.5	23	4.2	81	5.4	7	1.3
No	705	98.5	528	95.8	1434	94.6	517	98.7

a With or without radiotherapy.
b Includes radiotherapy only.

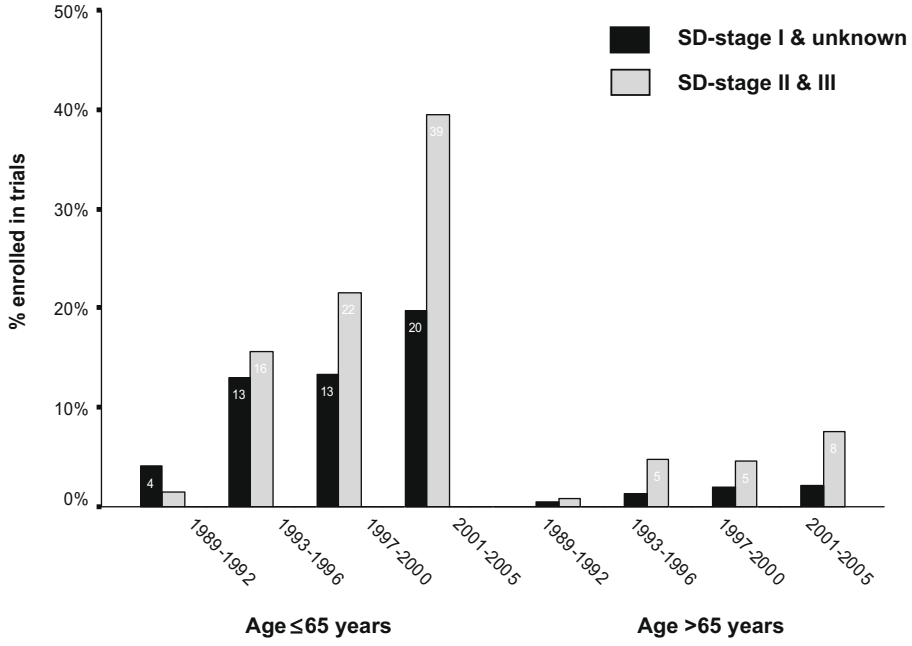

Fig. 2 – Trial participation according to period, SD-stage and age at diagnosis.

4. Discussion

This study showed major improvements in survival of younger patients with MM in the Netherlands since the mid-1990s. However, no improvement was seen among patients with MM aged over 65 years of age. The improving survival of the younger patients coincides with strongly increased trial participation and increased use of ASCT. Elderly patients with MM rarely received ASCT and participated far less frequently in clinical trials. It is unlikely that the improved survival in

Table 4 – Relative 3- and 5-year survival according to patient and tumour characteristics by patient age.

	All patients		Age ⩽65 years		Age >65 years	
	3-year (%)	5-year (%)	3-year (%)	5-year (%)	3-year (%)	5-year (%)
Total	47.0	29.9	61.3	42.5	39.0	22.7
Gender						
Male	48.1	31.3	60.7	42.6	39.1	23.0
Female	45.8	28.4	62.1	42.4	38.9	22.4
p-Value	*0.091*		*0.430*		*0.881*	
Age						
18–49	70.2	51.4	70.2	51.4	–	–
50–65	59.2	40.4	59.2	40.4	–	–
66–74	45.2	26.4	–	–	45.2	26.4
⩾75	33.8	19.5	–	–	33.8	19.5
p-Value	*<0.001*		*<0.001*		*<0.001*	
Period						
1989–1992	46.7	27.5	57.6	33.8	40.8	24.1
1993–1996	44.9	27.9	53.7	34.3	40.2	24.4
1997–000	46.8	29.7	63.7	45.8	38.1	20.9
2001–005	49.1	35.5	67.8	55.7	37.4	21.9
p-Value	*0.111*		*<0.001*		*0.185*	
SD-stage						
Stage I	65.7	47.1	78.1	62.2	59.7	39.3
Stage II	48.5	30.6	65.7	47.3	39.9	22.1
Stage III	40.3	23.9	57.0	37.0	29.3	14.9
Unknown	41.0	24.8	49.0	30.0	37.9	22.7
p-Value	*<0.001*		*<0.001*		*<0.001*	
Treatment						
Chemotherapy[a]	43.8	25.5	54.1	35.0	38.4	20.2
Chemotherapy ANDCT[a]	77.3	56.8	77.4	56.8	–	–
No therapy/supportive therapy[b]	47.2	34.4	69.0	54.0	40.3	27.9
p-Value	*<0.001*		*<0.001*		*0.047*	
Trial participation						
Yes	66.3	49.7	71.2	53.1	51.3	39.5
No	45.0	28.0	58.9	40.1	38.5	22.1
p-Value	*<0.001*		*<0.001*		*0.002*	

a With or without radiotherapy.
b Includes radiotherapy only.

the younger age groups is associated with earlier diagnosis, as we found no evidence of a shift towards a more favourable stage distribution over time.

The lack of improvement in survival of elderly patients with MM is worrisome as almost 70% of all patients with MM belong to the elderly group and the number of elderly MM patients will only increase further due to the ageing of the Dutch population. Current study protocols still use stringent age limits for patient inclusion, with a division in study protocols for patients aged up to 66 and aged 66 years or over. As participating hospitals tended to use the standard arm of the study protocols as standard treatment for patients with MM, this age division in treatment policy will continue. In contrast to younger patients with MM until recently little progress was made in the treatment of elderly patients. Novel agents such as thalidomide were introduced only in the second half of 2002 for elderly patients.[18] This lack of new agents and new treatment strategies also resulted in limited availability of clinical trials during the entire study period. Only 6% of the elderly patients were enrolled in clinical trials in the most recent period (2001–2005). In contrast for the younger patient group ASCT was already introduced during 1993–1996 and the first HOVON trial studying the effect of ASCT started in 1996.[15–17] And in the last decade several novel therapeutic agents entered the clinical arena including thalidomide and bortezomib.[10–12,18,22] Lenalidomide, a thalidomide analogue, recently entered clinical trials. However, the present analysis will not be affected by lenalidomide since the first clinical trials in our country started in 2007. The introduction of thalidomide and bortezomib as second line treatment since the early 2000s probably explains part of the strong prognostic effect of period of diagnosis for younger MM patients which remained after we adjusted for trial participation and ASCT. Supportive care has undoubtedly improved, making ASCT possible for an increasing number of patients. However it is unlikely that better supportive care

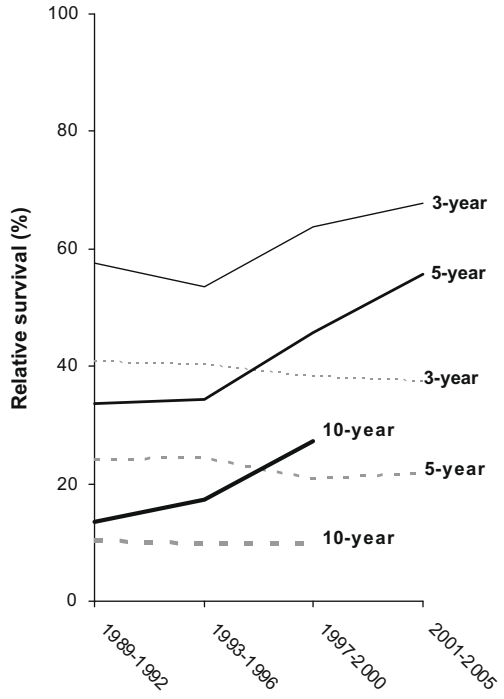

Fig. 3 – Relative 3-, 5- and 10-year survival of MM patients aged ⩽65 years (black line) and aged >65 years (grey dotted line) by period of diagnosis.

on itself has had a large effect on life expectancy for MM patients as we observed no increase in life expectancy for elderly patients despite improving supportive care.

Our findings are consistent with recent reports, using data from the US SEER registry and from Sweden, which also showed clear improvements in survival restricted to patients younger than 70 years and most prominent among patients younger than 60 years.[23,24] Also in these studies clear improvements were visible from the early 1990s onwards with the most marked improvements in the latest calendar periods. The EUROCARE study also demonstrated a clear improvement in survival of young MM patients. The 5-year relative survival in Europe increased from 38% during 1985–1999 to 53% during 1995–1999 for patients aged 45–54 years while for patients aged 65–74 years 5-year relative survival did not change (27% in 1985–1999 and 1995–1999).[25,26]

In our study more than 50% of stage I patients did not receive chemotherapy, irrespective of age. This is in line with the treatment guidelines in which chemotherapy is only indicated for MM with end-organ damage. A large proportion of the patients with stage I disease will, however, have received therapy following disease progression. Unfortunately treatment at progression was not recorded by the cancer registries. Therefore the reported proportion of patients receiving chemotherapy with or without ASCT is likely an underestimation of the true proportion of patients who received chemotherapy with or without ASCT in this population. This underestimation of the proportion of stage I patients receiving ASCT also partially explains the residual effect of period of diagnosis after adjusting for trial participation and ASCT.

Trial participation was associated with better survival, in part due to the patient selection required for trial participation and stricter follow-up which might translate into earlier or more aggressive second line treatment and thus in longer survival. Participating in clinical trials or receiving treatment in hospitals by clinicians who participate regularly in clinical trials has also been associated with better prognosis for other cancers.[27,28]

In summary our population-based study demonstrates a significant improvement in relative survival over time for younger patients with MM. For elderly patients no improvement was observed, probably due to the late introduction of new therapeutic agents. Now that these effective new agents have also become available for treatment of elderly MM patients, the stage is set for improving survival of elderly patients with MM.

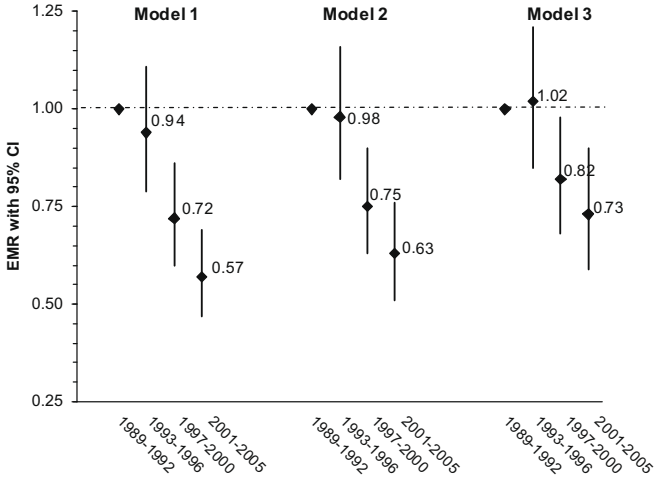

Fig. 4 – Excess Mortality Ratios (EMRs) for period of diagnosis for patients aged ⩽65 years. Model 1 adjusted for gender, age and SD-stage, Model 2 adjusted for gender, age, SD-stage and trial participation; Model 3 adjusted for gender, age, SD-stage, trial participation and treatment. The period 1989–1992 is used as reference period.

Table 5 – Multivariate excess mortality ratios (EMRs) after MM diagnosis stratified by age at diagnosis, adjusted for treatment.

	Age ⩽65 years			Age >65 years		
	EMR (%)	95% CI (%)	*p*-Value	EMR (%)	95% CI (%)	*p*-Value
Gender			*0.213*			*0.499*
Male	1.00			1.00		
Female	0.92	0.81–1.05		0.97	0.88–1.06	
Age			*0.001*			*<0.001*
18–49	1.00			–	–	
50–65	1.32	1.11–1.56		–	–	
66–74	–	–		1.00		
⩾75	–	–		1.44	1.31–1.57	
Period			*0.002*			*0.689*
1989–1992	1.00			1.00		
1993–1996	1.02	0.85–1.21		1.02	0.89–1.16	
1997–2000	0.82	0.68–0.98		1.06	0.93–1.21	
2001–2005	0.73	0.59–0.90		1.06	0.93–1.22	
SD-stage			*<0.001*			*<0.001*
Stage I	1.00			1.00		
Stage II	1.36	1.05–1.74		1.85	1.57–2.17	
Stage III	1.95	1.59–2.39		2.76	2.40–3.18	
Unknown	1.97	1.56–2.50		1.93	1.64–2.26	
Trial participation			*0.004*			*<0.001*
Yes	0.76	0.63-0.92		0.61	0.46-0.80	
No	1.00			1.00		
Treatment			*<0.001*			*<0.001*
Chemotherapy[a]	1.21	0.99–1.47		0.68	0.61–0.76	
Chemotherapy and ASCT[a]	0.73	0.56–0.95		–	–	
No therapy/supportive therapy[b]	1.00			1.00		

a With or without radiotherapy.
b Includes radiotherapy only.

5. Conflict of interest statement

None declared.

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