Outcome and survival of myeloma patients diagnosed 2008-2015. Real-world data on 4904 patients from the Swedish Myeloma Registry

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ABSTRACT

Epidemiology and outcome of myeloma are mainly reported from large university centers and collaborative groups, and do not represent 'real-world' patients. The Swedish Myeloma Registry is a prospective population-based registry documenting characteristics, treatment and outcome in newly diagnosed myeloma, including asymptomatic and localized forms, with the purpose of improving disease management and outcome. This report presents information on patients diagnosed between 2008 and 2015, including data on first-line treatment in patients diagnosed up to 2014, with a follow up until December 2016. We present age-adjusted incidence, patients' characteristics at baseline, treatment, response, and survival. Baseline data were available with a 97% coverage in 4904 patients (median age 71 years, males 70 years, females 73 years; 72% were 65 years or older), and at 1-year follow up in 3558 patients with symptomatic disease (92% of patients initially reported). The age-adjusted incidence was 6.8 myeloma cases per 100,000 inhabitants per year. Among initially symptomatic patients (n=3988), 77% had osteolytic lesions or compression fractures, 49% had anemia, 18% impaired kidney function, and 13% hypercalcemia. High-dose therapy with autologous stem cell transplantation was given to 77% of patients aged up to 66 years, and to 22% of patients aged 66-70 years. In the study period, 68% received bortezomib, thalidomide, and/or lenalidomide as part of the first-line treatment, rising from 31% in 2008 to 81% in 2014. In active myeloma, the median relative survival of patients aged 65 years or under was 7.7 years, and 3.4 years in patients aged 66 years and over. Patients diagnosed with myeloma in more recent years were associated with significantly higher rates of complete or very good partial remission ($P<0.05$), and with a significantly higher survival, with a Hazard Ratio (HR) of 0.84 (95%CI: 0.77-0.92; $P<0.05$). There was a small, but significant survival benefit in patients treated at university hospitals (HR 0.93; 95%CI: 0.87-0.99; $P<0.05$). We report here on a near complete 'real-world' population of myeloma patients during an 8-year period; a period in which newer drugs were implemented into standard practice. The overall incidence and median age were both higher than in most previous studies, indicating a more complete coverage of older patients. Myeloma survival in Sweden is comparable to other large registry studies, and responses and survival improved during the study period.

Introduction

Over recent decades, new treatment options have emerged in myeloma, with great expectations of improved survival. The introduction of high-dose melphalan with autologous stem cell support (HDM-ASCT) and newer drugs, such as the immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide), proteasome inhibitors (bortezomib and carfilzomib), monoclonal antibodies, and other classes, has led to a rapid implementation of these drugs under international guidelines.[1-7] To date, most studies on myeloma are based on selected patients from large referral centers and collaborative groups, with defined inclusion and exclusion criteria. But these often omit elderly patients, and thus do not reflect the true 'real-world' population.[8] Also, there is limited information available on the use of new therapies and their efficacy and tolerability in standard practice, supporting the need for representative population-based prospective studies on characteristics, diagnostics, treatment and outcome in myeloma patients.

Survival data from cancer registries are available, but often lack information on baseline characteristics and treatment. EUROCARE, covering nearly 50% of patients diagnosed with plasma cell neoplasms in Europe in the period 2000-2007, reports an age-standardized 5-year relative survival (RS) of 39.2%, an increase from 29.8% in 1997. Outcome was significantly better in the younger patients (68.6% *vs.* 21.8% 5-year relative survival), and in women (40.4% *vs.* 38.1%).[9] These results have later been confirmed by other cancer registry data.[10-12]

A 2010 Swedish study of retrospective data regarding baseline characteristics and treatment of consecutive patients in Malmö found a similar trend in improved survival, which correlated with the introduction of new treatment modalities.[13,14]

The Swedish Myeloma Registry was established in 2008, and the first Swedish guidelines on diagnostics and treatment of myeloma were published in 2010. This is the first report on our population-based data on characteristics, treatment and survival in Swedish myeloma patients diagnosed from January 2008 through December 2015.

Methods

The Swedish Cancer Registry

The Swedish Cancer Registry is a nation-wide compulsory dual-report system developed in 1958, which is supported by the personal identification code system used for all Swedish citizens which was established in 1947. First, all pathology specimens indicating malignancy are reported by the pathologist to the Regional Tumor Registry. Second, data on date and type of cancer diagnosis of all patients with a newly diagnosed cancer are reported by clinicians, with missing data actively requested to secure a high level of completeness. In a validation study, the completeness (95%) and diagnostic accuracy (98%) of the Swedish Cancer Registry was found to be very high for multiple myeloma patients.[15]

The Swedish Myeloma Registry

The Swedish Cancer Registry comprises web-reported clinical and laboratory data on all patients diagnosed with active myeloma, smoldering myeloma, plasma cell leukemia, and solitary bone and extramedullary plasmocytomas in Sweden since 2008, at time of diagnosis and after a 1-year follow up. Coverage is analyzed through the compulsory Swedish Cancer Registry. Survival data are obtained from the Swedish Population Registry. Patients diagnosed by autopsy are included in the Swedish Cancer Registry, but not in the Swedish Myeloma Registry. The registry is publicly financed, and the patients are reported by treating physicians and nurses. Courses are held for those responsible for reporting patient data to assure coherent reporting in all regions and hospitals. These courses cover inclusion criteria, parameters, and the manual of the Swedish Myeloma Registry. Criteria for the diagnosis of active myeloma (MM), smoldering myeloma (SMM), plasmocytoma, and plasma cell leukemia are defined according to the International Myeloma Working Group (2003).[16] Other gammopathies, such as monoclonal gammopathy of undetermined significance (MGUS) and AL-amyloidosis are not included in the registry. Age-specific incidence, age distribution at diagnosis, median time from diagnosis to registry report, and distribution of the diagnoses in the registry are reported. Adherence to treatment guidelines concerning diagnostics and ISS-staging (International Staging System) is checked by studying the use of different diagnostic tools such as bone marrow sample, cytogenetics including fluorescence *in situ* hybridization (FISH), β 2-microglobulin (β_2m) and s-albumin. Baseline characteristics at diagnosis are collected, including M-protein isotype, percentage of plasma cells in the bone marrow, serum free-light chain (FLC), and laboratory parameters capturing CRAB criteria (CRAB; Calcium, Renal insufficiency, Anemia or Bone lesions). One year after diagnosis of symptomatic MM, data on first-line therapy, occurrence and date of first relapse or complications are requested. The study was performed in agreement with the ethics committee of Stockholm and the Swedish Society of Hematology.

Table 1. Characteristics of active myeloma (MM) and smoldering myeloma (SMM) patients in the Swedish Myeloma Registry.

Characteristics	Patients
Total, n (%)	4904 (100%)
Diagnosis, n (%)	
Multiple myeloma	3988 (81.3%)
Smoldering multiple myeloma	916 (18.6%)
Age in years at dx, median	
All	71
Male	71
Female	73
Immunoglobuline class n (%)	
IgG	2882 (58.8)
IgA	1033 (22.3)
Bence-Jones MM	688 (14.0)
Non-secretory MM	143 (2.9)
IgD	19 (0.4)
IgM	14 (0.3)
Not known	23 (0.5)
More than one Ig	41 (0.8)
IgE	1 (0.0)

n: number; dx: diagnosis.

Treatment of MM in Sweden

In Sweden, patients with myeloma are typically diagnosed and followed clinically by physicians at hospital-based hematology centers, and no patients are seen at private hospitals. In the study period, the treatment of MM was guided by the British/Nordic

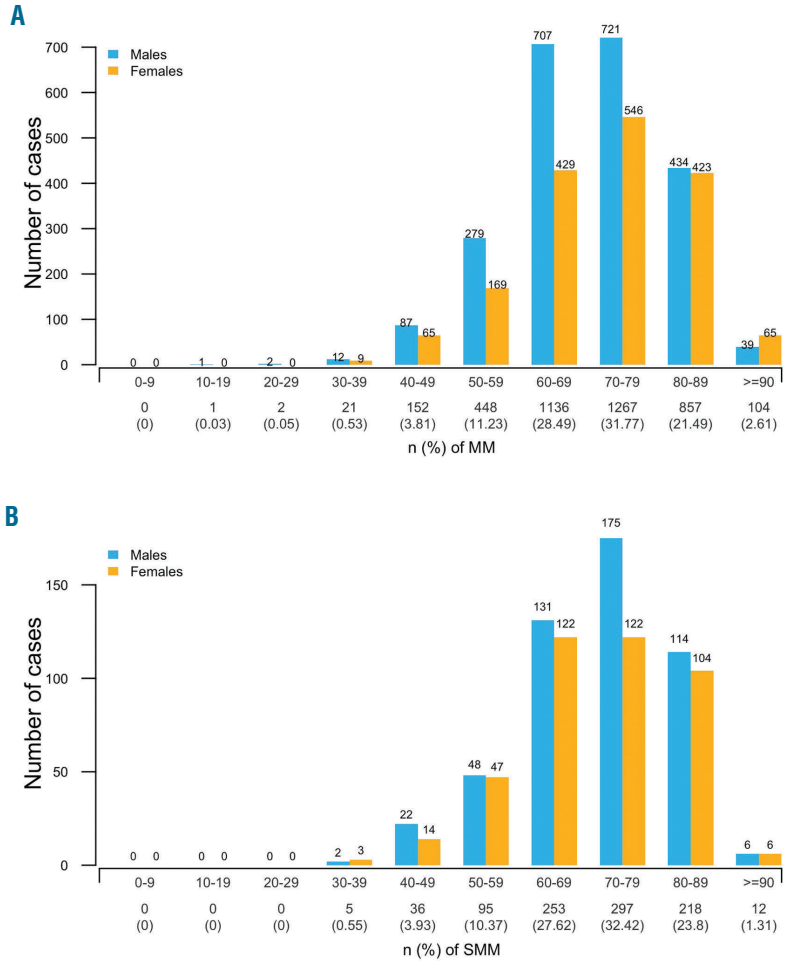

Figure 1. Age distribution in the Swedish Myeloma Registry in men and women in (A) active myeloma (MM) and (B) smoldering myeloma (SMM). n: number.

treatment program for multiple myeloma (2005),[17] and the Swedish 2010 National Guidelines (up-dated in 2013). Briefly, high-dose melphalan and autologous transplantation (HDM-ASCT) was recommended as up-front treatment for all MM patients aged 65 years or under, and in patients aged 66-70 years if they had good performance status. In 2005, vincristine, adriamycin, and dexamethasone (VAD) or similar combinations were recommended as induction treatment before HDM-ASCT, and later, in the 2010 guidelines, bortezomib and thalidomide became part of standard induction, following an introduction period subsequent to approval in 2004. Patients at smaller hospitals are, as a rule, only referred to university hospitals for the ASCT procedure and afterwards return to their hospital of origin. For patients aged 66 years and older, melphalan and prednisone (MP) or cyclophosphamide and dexamethasone (CyDex) was standard up-front treatment until 2004 when melphalan, prednisone and thalidomide (MPT) was incorporated as a treatment option. In 2010, MPT was the standard for patients not eligible for ASCT, and MP and bortezomib (MPV) were treatment options. In the 2013 version, both MPT and MPV were standard up-front treatments in those patients not eligible for ASCT.

Table 2. Prevalence of myeloma-related organ and tissue impairment (ROTI) and International Staging System (ISS) stage at diagnosis in patients with active myeloma at diagnosis in the Swedish Myeloma Registry.

	Patients n=3988
ROTI (%)	
Anemia*	49%
Renal impairment**	18%
Hypercalcemia***	13%
Skeletal disease	77%
ISS stage (%)	
Stage I	23
Stage II	44
Stage III	33

n: number; in patients with report on: *anemia defined as hemoglobin < 10g/dL and reduction of 2g/dL from the normal value; **renal failure defined as creatinine >173 mol/L; ***hypercalcemia defined as s-calcium (uncorrected) > 2.75 mmol/L or ionized calcium>1.45 mmol/L.

Statistical analysis

Incidence was extracted from the Swedish National Board of Health statistical database on cancer 1970-2015, which includes all patients with the diagnosis ICD 203*.[18] All other analyses were performed on patients reported to the Myeloma Registry with a 97% coverage compared to the Swedish Cancer Registry.[19] For diagnoses of MM and SMM, we summarized descriptive statistics at diagnosis. We tabulated categorical variables such as sex, Ig-class and use of new drugs. Summary statistics, for example, median and range, were calculated for continuous variables such as age and β_2M. The χ^2 test was used as significance test of difference in proportions. Statistical analysis of treatment was only carried out on MM patients with a reported 1-year follow up, including patients who had developed symptomatic disease after SMM

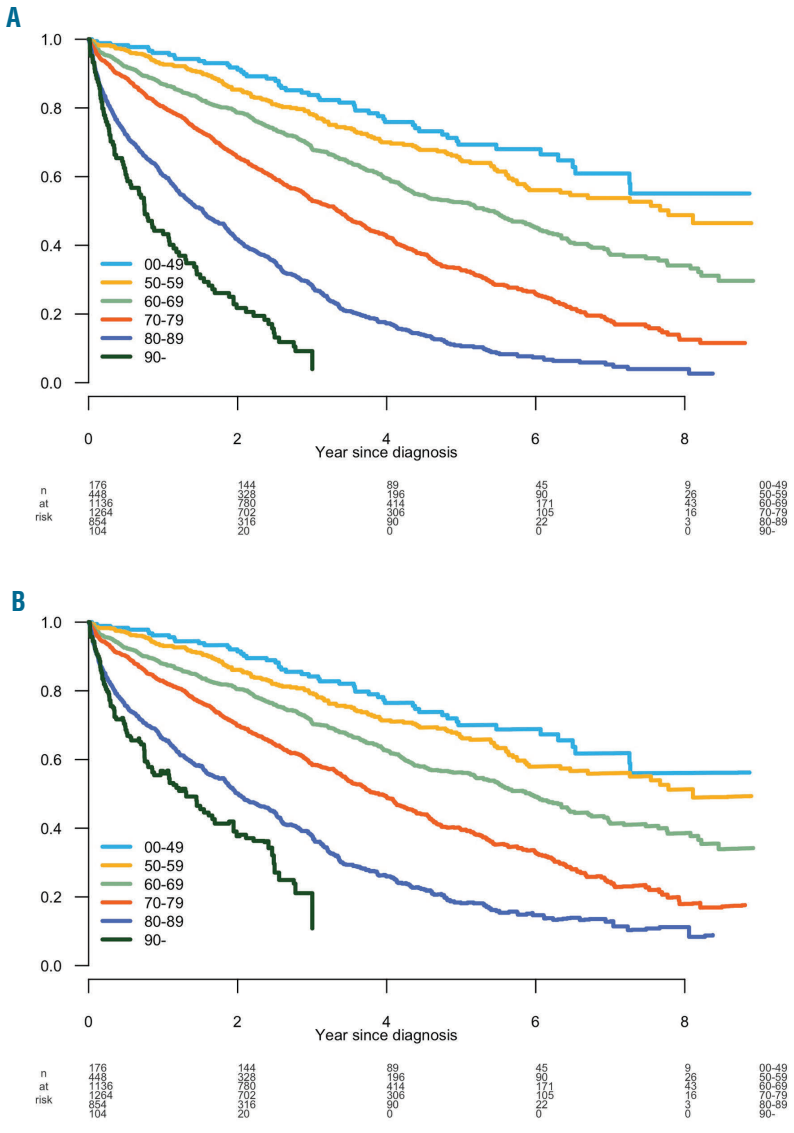

Figure 2. Survival in active myeloma (MM) in the Swedish Myeloma Registry: observed (A) and relative (B) survival, by 10-year age cohorts. n: number.

or plasmacytoma. We estimated observed survival using the Kaplan-Meier method. When estimating relative survival (RS), relative to the general Swedish population, we used the Ederer II method for expected survival. For observed survival (OS), we estimated Hazard Ratios (HR) using Cox proportional hazards regression modeling. Also for RS, we estimated HR using proportional hazards regression, but in transformed time.[20] Survival time was calculated from date of diagnosis to death or censoring. Patients were censored at the end of follow up in the study or loss to follow up. Age-standardized RS was calculated in each age group separately and then weighted together using weights from a standard population, in this case, the International Cancer Survival Standard (ICSS) 1. We used a proportional hazard model of RS by year of diagnosis in all patients to estimate changes in survival over time. The survival analysis by year of diagnosis included both SMM and MM, and the date of diagnosis refers to the date of the primary diagnosis, whether this was SMM or MM. To evaluate the impact of the treating hospital, we estimated a proportional hazard model of RS by hospital type, in the categories "university hospital" or "not", and hospitals reporting treatment on more or less than 10 patients per year. The survival analysis by treatment response and by hospital type was carried out on symptomatic MM patients only (including patients who had developed symptomatic disease after SMM or plasmacytoma) with reported 1-year follow up, to enable comparison with statistics on treatment. When adjusting for ISS stage in regression analysis, we treated patients with missing values in the stage variable as a category within the ISS stage variable in order to not exclude the cohort of patients with missing data on ISS stage. $P<0.05$ was considered statistically significant. All data preparation and analysis were carried out using R statistical software.[21]

Results

A total of 5222 patients with plasma cell diseases diagnosed in the period 2008-2015 had been reported to the Swedish Myeloma Registry as of December 31st 2016, with 97% coverage when compared with the Swedish Cancer Registry.

Clinical data at diagnosis were available for 4904 MM and SMM patients diagnosed in the period 2008-2015

Table 3. Proportion of patients who received novel drugs (thalidomide, bortezomib or lenalidomide) as first-line line treatment among active myeloma patients with reported follow up, by year of diagnosis and by age group (-65, 66–80, >80) years in the Swedish Myeloma Registry.

Patients with novel drugs first line	All ages n=2400 (%)	≤65 years n=913 (%)	66-80 years n=1212 (%)	>80 years n=275 (%)
2008-2014	67.5	81.3	72.6	35.6
2008	31.1	24.4	42.0	17.7
2009	56.1	76.8	55.7	24.8
2010	69.1	91.6	74.1	32.6
2011	75.2	93.8	76.0	34.5
2012	77.0	98.1	83.3	37.3
2013	81.0	95.6	88.1	49.2
2014*	81.1	92.2	86.2	54.3

*2014 has less follow up on patients reported (at data cut off 78.7% of initially reported).

Table 4. Proportion with very good partial remission (VGPR) or better among active myeloma patients with reported follow up after first-line treatment in patients diagnosed 2008-2014 in the Swedish Myeloma Registry, by year of diagnosis and by age group (-65, 66-80, >80 years).

Patients VGPR or better	All ages n (%)	≤65 years n (%)	66-80 years n (%)	>80 years n (%)
2008-2014	1415 (45.8)	725 (68.3)	575 (38.9)	115 (20.8)
2008	152 (36.1)	87 (55.1)	56 (28.0)	9 (14.3)
2009	173 (40.3)	97 (62.2)	58 (23.4)	18 (23.4)
2010	209 (47.5)	104 (67.5)	86 (43.9)	19 (21.1)
2011	223 (45.4)	123 (72.4)	91 (35.1)	9 (14.5)
2012	223 (46.4)	114 (73.5)	91 (39.6)	18 (18.8)
2013	230 (51.6)	117 (78.0)	94 (46.8)	19 (20.0)
2014*	205 (53.5)	83 (70.3)	99 (50.5)	23 (33.3)

*2014 has less follow up on patients reported (at data cut off 78.7% of initially reported).

(Table 1), and at 1-year follow up for 3558 of all MM cases diagnosed 2008-2014, being 92% of all MM initially reported 2008-2014. Data were reported from 74 different centers in Sweden, approximately 40% from university hospitals, and 60% from regional and smaller hospitals, all public care institutions. The median time of follow up of all SMM and MM patients was 4.9 years.

The total crude and age-adjusted (to the population in Sweden in the year 2000) incidence was 7.0 and 6.8 cases per 100,000 inhabitants, respectively (8.0 and 8.2 for men, and 6.0 and 5.3 for women per 100,000 inhabitants, respectively). The corresponding incidences for European and World standard populations are 4.8 and 3.2, respectively. Due to the difference in age distribution in the population, the total number of women was higher in the cohort aged over 85 years (Figure 1). However, the age-specific incidence was higher amongst men in all ages, and the difference increased with advancing age (Online *Supplementary Figure S1*). The median age of patients reported to the registry with a diagnosis of MM or SMM was 71 years (70 years for men and 73 years for women; 71 years for all MM and 72 years for all SMM). Twenty-four percent of patients were 80 years or older at the time of diagnosis. Notably, the percentage of patients aged under 65 years was 28.3%; 61.4% of these were men and 38.6 women.

Baseline characteristics

Serum protein electrophoresis was performed in 99.5% of all patients and a skeletal survey was performed in 97%. A bone marrow sample was taken in 97% of patients at diagnosis, with a median of 27% plasma cells in MM patients and 15% in SMM. Among patients with MM at diagnosis (n=3988), 77% had reported osteolytic lesions and/or compression fractures at diagnosis, and this did not increase over the study period. Anemia was seen in 49%, renal insufficiency (s-creatinine >173 μmol/L) in 18%, and creatinine levels more than 110 μmol/L were reported in 33% of MM patients. Hypercalcemia was reported in 13% of MM patients at the time of diagnosis (Table 2). The number of patients aged 80 years and under who had FISH performed at diagnosis increased over the study period, from 30% in the period 2008-2010, to 43% in 2011-2015. Staging according to the ISS was reported in 71% of patients with MM in the study period. In MM patients with reported ISS-stage, 23% were ISS stage I, 44% stage II, and 33% stage III (Table 2).

Treatment

Of all patients with reported follow up, 77% of patients aged 65 years or under at diagnosis and 5% of patients aged over 66 years received HDM-ASCT as first-line treatment. In patients aged 66-70 years, HDM/ASCT was performed in 22%. Allogeneic transplantation as part of first-line treatment was performed in only 1% of patients in

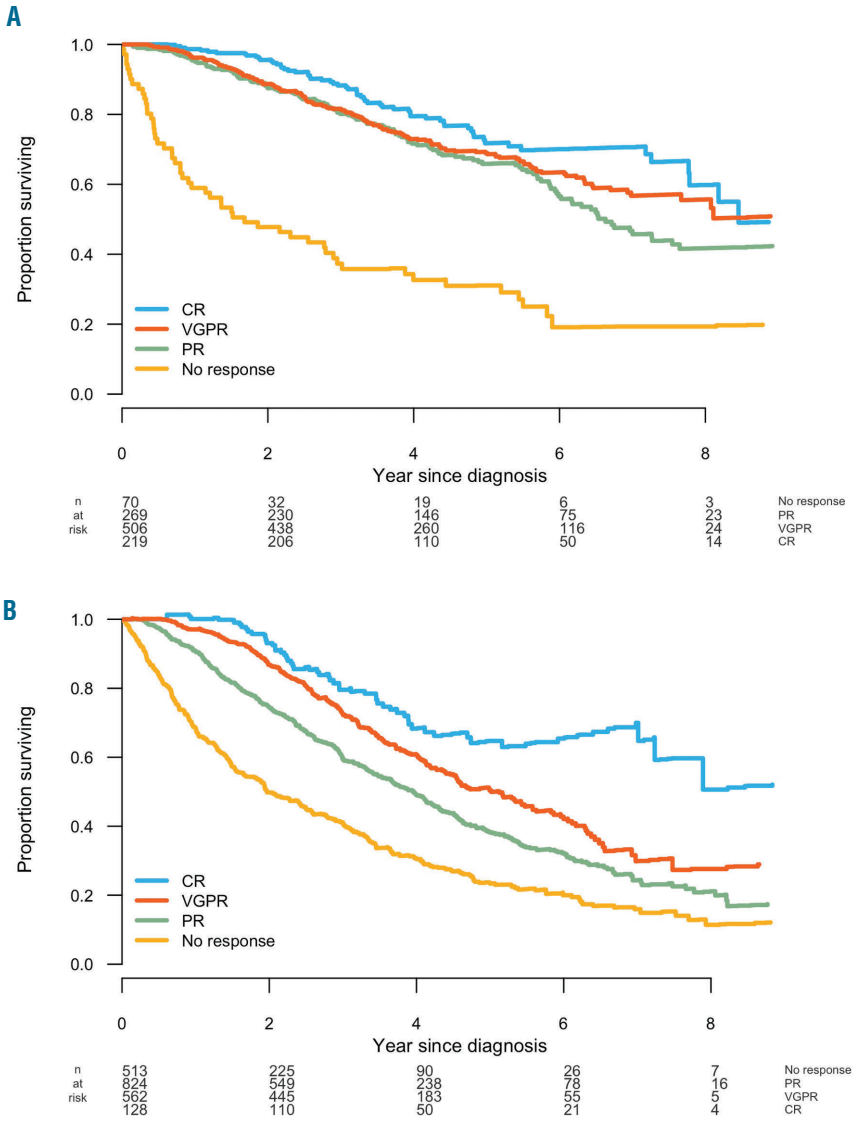

Figure 3. Relative survival in active myeloma (MM) by treatment response in the Swedish Myeloma Registry in age cohorts: (A) under 65 years of age and (B) 66 years of age and over. CR: complete remission; VGPR: very good partial remission; PR: partial remission; n: number.

the study period. A total of 5.2% of reported MM patients did not receive any anti-myeloma treatment the first year after diagnosis and, notably, this involved 11% of patients over 80 years of age. Bisphosphonates were given in 79% of patients aged 65 years or under, and in 67% in patients over 65 years of age. There was an increase in the use of one or more of the novel drugs (thalidomide, lenalidomide, and bortezomib) over the study period (Table 3).

Response

The proportion of patients achieving very good partial remission (VGPR) or better after first-line treatment increased from 36% in patients diagnosed in 2008 to 54% in 2014 ($P<0.05$). The increase was seen in all age groups, but was more pronounced in patients aged over 80 years, where the proportion of patients reaching VGPR or better rose from 14% to 33% (Table 4).

Survival in all myeloma patients

The 1-, 3-, and 5-year OS in all patients (SMM+MM) was 81%, 59%, 42%, and the corresponding RS was 84%, 65%, and 49%, respectively. Survival in 10-year cohorts in all myeloma patients is shown in *Online Supplementary Table S1 and Figure S2*. Early death (<1 year after diagnosis) was observed in 19% of patients. The 3-year RS was 62% (95%CI: 59.7-64.6) in women, and 67% (95%CI: 65.0-69.3) in men. After age standardization, the 3-year RS in women was 67% (95%CI: 65.1-69.6) and 70% in men (95%CI: 67.8-71.8). Survival per SMM and MM diagnosis is shown in *Online Supplementary Tables S2 and S3*.

Survival in MM

In patients with MM and reported follow up (n=3558), the median OS varied considerably depending on age at diagnosis, ranging from 7.8 years in patients aged 60 years and under, to 1.5 years for patients aged 80-89 years (*Online Supplementary Table S4*). After a median follow up of 5.5 years, the median OS in the youngest cohort (<50 years) had not yet been reached (Figure 2). The median RS of patients aged 65 years or under was 7.7 years, and 3.4 years in those aged 66 years and over. The 5-year OS and RS in MM patients was 38.3% and 44.9%, respectively. The median RS according to ISS stage was 3.2 years and 5.6 years for stages III and II, and 8.2 years for stage I. Patients with no reported stage had a similar median RS as stage III patients of three years.

Survival according to response

Overall, better response to first-line treatment was significantly associated with superior survival ($P<0.05$) (*Online Supplementary Table S5*). In younger patients, there was no significant difference in 5-year RS in patients in PR, VGPR and CR (Figure 3)

Survival according to year of diagnosis

Patients diagnosed in the period 2011-2015 had a trend to better 1-, 3- and 5-year RS compared to patients diagnosed 2008-2010. In patients aged over 65 years, this trend was more evident than in younger patients (*Online Supplementary Tables S5 and S6, and Figure S3*). In a proportional hazard model of RS by year of diagnosis in all patients, later calendar year of diagnosis was significantly associated with improved RS, with an HR of 0.93 (95%CI: 0.92-0.95; $P<0.05$).

Survival according to treating hospital

The 1, -3 – and 5-year survival was significantly higher in university hospitals (*Online Supplementary Table S7*). In a proportional hazards model for the RS, the HR was 0.93 (95%CI: 0.87-0.99; $P<0.005$). Even when adjusting for age, sex, and ISS-stage, the HR was of borderline statistical significance (HR=0.91; 95%CI: 0.83-1.0; $P=0.04$). Similar results were obtained when analyzing centers that treated 10 or more MM patients per year (*data not shown*).

Discussion

In this study from the Swedish Myeloma Registry, we report incidence, baseline characteristics and survival of an unselected population comprising more than 97% of all myeloma patients diagnosed in Sweden in the period 2008-2015. We found an age-adjusted incidence of 6.8 per 100,000 inhabitants; this translates into 4.8 and 3.2 per 100,000 inhabitants in European and World standards, respectively. This is higher than figures previously reported by most population-based studies,[22,23] but is in agreement with data from a previous large Swedish study.[24] The high age-adjusted incidence might be explained by better case ascertainment in the elderly. Overall, the proportion of elderly (65 years and older) myeloma patients at diagnosis was 72%, and this exceeds the number of reported elderly patients in most known registries today, but is supported by population-based data from the Danish Myeloma Registry[25] and a recent report on a large cohort of European patients.[26] We observed a median age of 71 years at diagnosis, which is higher than other myeloma studies,[8] and a steep increase in age-specific incidence extending to the oldest age cohorts. This indicates that our population, given the very high coverage provided by the Swedish Myeloma Registry, reflects the 'real-world' situation in myeloma today.

Our study shows encouraging survival rates in the MM population. In our population-based study, the 5-year OS was 38%, similar to the data from the EUROCARE study.[27] In a 2014 report from the Mayo clinic based on 1084 MM patients (median age 66 years), the median OS from diagnosis was 5.2 years and the 6-year OS estimate was 45%.[8] We show that with the increased use of novel agents there was an improvement in response rates. We also show that, over the study period, the proportion of elderly patients receiving novel drugs increased. The difference in survival between the different age cohorts was less pronounced in RS compared to OS, which demonstrates the importance of including RS in survival analyses in MM.

In the European Registry data from 2008 (EUROCARE),[28] a 2% survival advantage was seen in women. However, in our more recent study covering the period from 2008 to 2015, after age standardization, there was no difference in survival between men and women.

As expected, and as shown before,[29,30] achievement of response was predictive of prolonged survival. There was a significant difference in survival in patients aged over 65 years. Given this, we investigated the impact of response grade on survival in different age cohorts in patients with MM at diagnosis. The analysis revealed that responding patients in all age groups had a better outcome than non-responding patients, and that patients achieving CR had the longest survival. However, interestingly, in patients aged 65 years or under there was no significant difference in survival according to the degree of response (CR, VGPR or PR). This is contrary to results from many randomized studies,[31-33] and may indicate that achievement of a high quality response to first-line treatment may not have the same importance for survival in a young, unselected myeloma population where the majority of patients will eventually receive multiple lines of treatment.

We found a survival benefit in patients reported from university hospitals and those hospitals treating a large number of MM patients. This is not surprising given the speed of progress in diagnostics and the new treatments of recent years, and has, in fact, also been reported in other studies.[34,35] We could not detect a significant difference in referral patterns, but in spite of this, our results should be interpreted with caution, as residual confounding factors may have influenced outcome. However, this does underline the importance of high volume centers with expert knowledge in MM treatment and the need for further studies to monitor access to care for myeloma patients.

The strength of this study is the large, population-based cohort and excellent coverage provided by the Swedish Cancer Registry. Another strength is the public Swedish health care system. In Sweden, all patients with a diagnosis of cancer are treated in public hospitals, enabling publicly financed and equal treatment for all MM patients; this reduced the risk of information- and selection-bias in this study. The Swedish Myeloma Registry has provided valuable information on how new treatments have been introduced and have been established as standard of care in clinical practice, leading to improved response rates in all age groups. Importantly, we have been able to show that there is good adherence to guidelines in all regions of Sweden, both with regards to diagnostics and to management, and the registry has helped define areas where improvement is needed. The proportion of patients with prognostic classification according to ISS and for whom FISH was performed as part of diagnostic workup has increased; however, FISH has still not been established as standard clinical practice in all hospitals. One limitation is that treatment data on 8% of patients were incomplete, and some baseline characteristics, such as ISS-stage, were also missing. In addition, we do not have detailed data on cytogenetics and comorbidities. Finally, we did not have sufficient follow-up data to perform analyses on progression-free survival after first-line treatment, which is a further limitation of this study.

Many large and important studies on characteristics and

survival in MM patients are compromised by the reporting bias of referral centers, either because they are university hospital registries with a low median age at MM diagnosis, or because they report on selected patients in clinical trials who do not necessarily, therefore, reflect the 'real-world' scenario in myeloma. Great efforts are being made to ensure the data available in the Swedish Myeloma Registry are complete, and to present population-based data on management and outcome in Sweden. However, we can now present a near complete 'real-world' population of myeloma patients, and show that the overall incidence and median age is higher than in most previous studies, indicating a more complete coverage of older patients. Myeloma survival in Sweden was similar to other large registry studies, and responses and survival improved over the study period.

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