bjh research paper

Survival of multiple myeloma patients in the era of novel therapies confirms the improvement in patients younger than 75 years: a population-based analysis

Samantha Pozzi,[1] Luigi Marcheselli,[1,2] Alessia Bari,[1] Eliana V. Liardo,[1] Raffaella Marcheselli,[1] Stefano Luminari,[3] Micol Quaresima,[3] Claudia Cirilli,[2] Paola Ferri,[4] Massimo Federico[2,3] and Stefano Sacchi[1]

[1]Programme of Innovative Therapy in Oncology and Haematology, Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, [2]Modena Cancer Registry, [3]Medical Oncology, Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, and [4]Nursing School, Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy

Received 26 March 2013; accepted for publication 3 June 2013

Correspondence: Samantha Pozzi, MD, Programme of Innovative Therapy in Oncology and Haematology, Department of Diagnostic, Clinical and Public Health Medicine, Centro Oncologico, Policlinico di Modena, Largo del Pozzo 71, 41124 Modena, Italy.
E-mail: samantha.pozzi@unimore.it

Summary

Novel treatments for multiple myeloma (MM) have shown promising results in clinical trials, but the advantage in unselected patients is still unclear. In order to evaluate whether novel therapies impact survival of MM patients, we performed a population-based analysis on data collected by the Modena Cancer Registry from 1989 to 2009. The analysis evaluated 1206 newly diagnosed MM patients collected in the years 1988–96 (conventional therapy), 1997–05 (high dose melphalan and autologous transplant), and 2006–09 (novel agents era). Both relative survival (RS) and overall survival (OS) improved over the years, but not equally in the three groups. For patients aged <65 years, RS improved in 1997–05 and 2006–09 compared with previous years and a trend to improvement was observed from 1997–05 to 2006–09. For patients aged 65–74 years, RS improved significantly in 2006–09 compared with 1988–96 and 1997–05. No amelioration was observed for patients 75+ years old. OS confirmed RS. In conclusion, the survival of MM patients aged <65 and, in particular, 65–74 years, has improved over time, especially after 2006. This observation provides circumstantial evidence that novel therapies might impact patient survival. Despite the limits of this study, these data refer to an unselected population, giving a picture of every day clinical practice.

Keywords: multiple myeloma, survival, population study, epidemiology, therapy.

Multiple myeloma (MM) is a neoplastic disorder of the bone marrow that results from the monoclonal proliferation of plasma cells. It represents 13% of all haematological cancers and approximately 1% of all types of cancers (Palumbo & Anderson, 2011), with European Age-Standardized (AS) Incidence Rates of 5·4 per 100 000/year in males and 3·8 per 100 000/year in females (http://www.cancerresearchuk.org/cancer-info/cancerstats/, last accessed 20 May 2013) and 7·4 per 100 000/year and 4·7 per 100 000/year cases in males and females, respectively, in the United States (http://seer.cancer.gov/statfacts/html/mulmy.html). The European AS Incidence Rates per 100 000 Population in UK in 2009 overlaps with the US and European data, corresponding to 7·1 and 4·3 cases per 100 000 in males and females, respectively (http://www.cancerresearchuk.org/cancer-info/cancerstats/, last accessed 20 May 2013). The approximate Italian incidence is a little higher, at 9·5 per 100 000 in males and 8·1 per 100 000 in females (http://www.registri-tumori.it). In 2009 the raw incidence rate in the province of Modena was 10 cases per 100 000 inhabitants per year (10·6 in males and 9·9 in females respectively) (http://www.rtm.unimo.it/Pubblicazioni.html). The survival of MM patients ranges from less than 6 months to more than 10 years depending on stage of the disease at diagnosis and prognostic factors (Greipp *et al*, 2005). Despite improvements in treatment, MM is still characterized by frequent relapses and ultimately patients die due to disease progression, with MM accounting for approximately 1·9% of cancer mortality (Jemal *et al*, 2008). In 2009 the raw mortality rate in the province of Modena was 2·4 and 4·2 per 100 000 in males and females respectively (European AS rate, 1·3 and 2·0 per 100 000 in males and females, respectively). Death rates for all types of cancers have

First published online 27 July 2013
doi: 10.1111/bjh.12465

decreased significantly in the past 20 years, even in MM patients where the death rate has decreased from 4·83 per 100 000 in 1990 to 4·39 per 100 000 in 2007 in men, and from 3·26 per 100 000 in 1991 to 2·81 per 100 000 in 2007 in women (Siegel *et al*, 2011). In the same way, the life expectancy of MM patients has improved over the past 50 years, especially following the introduction of melphalan in the clinics in the 1960s, high-dose melphalan followed by autologous stem cell support (HDM/ASCT) in the 1980s and, more recently, innovative therapies. Before the introduction of alkylating agents median MM patient survival was <1 year (Greenlee *et al*, 2000) and the current expected survival is estimated to be 5–7 years in patients receiving HDM/ASCT, and 3–4 years in patients receiving conventional chemotherapy (Ludwig *et al*, 2008). In England, the 5-year survival has improved in the last 40 years, in both sexes, from 11–12% to over 37% (http://www.cancerresearchuk.org/cancer-info/cancerstats/). The improvement in survival has been analysed in detail (Kumar *et al*, 2008, 2012; Ludwig *et al*, 2008; Campagnaro *et al*, 2011). However, the data very often referred to selected patients enrolled in clinical trials or tertiary institutions and cannot be easily generalized. In order to evaluate how significantly the introduction of HDM/ASCT and novel therapeutic approaches had affected the survival of myeloma patients we analysed the overall survival (OS) and Relative Survival (RS) in the Province of Modena between 1988 and 2009 based on the data collected by the Modena Cancer Registry (MCR). We also reported the trend for calendar years at diagnosis (from 1988 to 2009) of the RS at 3 years, with the projection of the linear fit at the period of diagnosis 2006–09. Sixty-three percent of data collected by MCR came from a university hospital and 37% were from local institutions that were not tertiary referral centres. Compared with results obtained from Clinical Trials, data from Registries give a better picture of every-day clinical practice.

Materials and methods

Modena Cancer Registry is a member of the Italian Cancer Registry Association (AIRT) and the International Association of Cancer Registry (IACR). MCR collects data regarding cancers diagnosed in the province of Modena (Italy). This study used data collected between January 1, 1988 and December 31, 2009; data regarding date of death up to June 30, 2011 (end of follow-up) was also utilized.

According to Italian Law, ethic committee approval was not required for this study because all information was collected and used only for anonymous and aggregate statistical analysis.

For the current analysis the following criteria were applied to the study: International Classification of Diseases (ICD)-03 (morphology codes 9731-9732, 9734) and sex. Patients were divided based on age and year of diagnosis. As HDM/ASCT became a standard treatment for MM in the province of Modena in 1996 and thalidomide was introduced in our clinical practice between 2002 and 2003, followed by bortezomib and lenalidomide after 2005, three periods of time were considered: 1988–96 (conventional therapy), 1997–05 (HDM/ASCT), 2006–09 (HDM/ASCT and novel agents era). Age was also taken into account as a prognostic factor and patients were divided into three groups: younger than 65 years of age (with 65 representing the cut-off for HDM/ASCT in our clinical practice); between 65 and 74 years; and 75 years or older.

The analysis was directed to the determination of the estimated OS evaluated by Kaplan–Meier method and modelled with the Cox proportional hazard regression analysis (Cox, 1972) and the RS. RS is defined as the observed survival, where all deaths are considered events, divided by the expected survival of a comparable group from the general population, which is assumed to be free from MM. Expected survival was estimated using the Ederer II method (Ederer & Heise, 1959) and based on the Italian National Institute of Statistic (ISTAT) life tables stratified by age, sex and calendar period. Five-year RS with 95% confidence interval (95% CI) was calculated for patients diagnosed during three calendar periods: 1988–96, 1997–05 and 2006–09. The excess mortality was modelled with the Poisson regression (Dickman *et al*, 2004) and the parameter estimates from this model are interpreted as excess mortality rate ratio (RR). Linear fit was obtained from a simple linear regression and the projection at the period 2006–09 was estimated by means of the regression coefficient of the linear fit. An exploratory analysis with restricted cubic spline regression using different degrees of freedom had shown the linear function as the best fit of the present data. The completeness of the follow-up was checked by the method proposed by Wu *et al* (2008). All reported tests were two-sided. The *P*-value was considered statistically significant when $\leq 0{\cdot}05$.

Results

From 1988 to 2009, 1206 patients affected by MM were diagnosed in province of Modena. Sex distribution was homogeneous (616 males and 590 females) in all the three periods analysed (Table I). No major differences of age at diagnosis were observed over time: 29%, 31% and 33% of patients were <65 years of age in the periods 1988–96, 1997–05 and 2006–09, respectively. A similar distribution was observed for patients aged 65–74 years (35%, 30% and 26% respectively) and 75+ years of age (36%, 39% and 41%) (Table I). The percentage of completeness of the data set at follow-up was 98%.

Overall, the 5-year RS (95% CI) showed a clear improvement from the period 1988–96 vs. 1997–05 and 2006–09, increasing from 45·7 to 49·9 to 55·7% respectively (Table II; Fig 1). These data are in accordance with the OS at 5 years, which improved from 37·7 to 42·5 to 50·9 in the three time frames analysed (Table III). Sex did not show any impact on survival (Table II). However the subset analysis by age showed that the improvement of both RS as well as OS was not equally distributed in the three groups.

Table I. Case series of multiple myeloma patients diagnosed in the province of Modena between 1988 and 2009.

	N	%	No. dead	Person-years	Rate (×100) (CI95%)
Period 1988–96					
Age group					
<65	128	29	109	955	11·4 (9·4–13·8)
65–74	153	35	145	845	17·2 (14·5–20·2)
75+	157	36	154	449	34·3 (29·1–40·2)
Gender					
M	236	54	222	1109	20·0 (17·5–22·8)
F	202	46	186	1140	16·3 (14·1–18·8)
Period 1997–2005					
Age group					
<65	159	31	67	1124	6·0 (4·6–7·6)
65–74	150	30	110	709	15·5 (12·8–18·7)
75+	196	39	179	508	35·2 (30·3–40·8)
Gender					
M	249	49	172	1125	15·3 (13·1–17·8)
F	256	51	184	1216	15·1 (13·0–17·5)
Period 2006–09					
Age group					
<65	86	33	12	215	5·6 (2·9–9·7)
65–74	68	26	16	140	11·4 (6·5–18·6)
75+	109	41	68	165	41·2 (32·0–52·2)
Gender					
M	131	50	47	266	17·7 (13·0–23·5)
F	132	50	49	254	19·3 (14·3–25·5)
Total					
Age group					
<65	373	31	188	2294	8·2 (7·1–9·4)
65–74	371	31	271	1694	16·0 (14·2–18·0)
75+	462	38	401	1122	35·7 (32·3–39·4)
Gender					
M	616	51	441	2500	17·6 (16·0–19·4)
F	590	49	419	2610	16·0 (14·6–17·7)

M, males; F, females. Rate = # dead/person-years ×100. Confidence intervals were estimated considering that the rate has a Poisson distribution.

This tables reports the data of patients affected by multiple myeloma (MM) collected by the Modena Cancer Registry (MCR) between 1988 and 2009. A total of 1206 patients were collected, with equal distribution by sex (M/F: 51% vs. 49%), and age (<65 years: 31%; 65–74 years: 31%; 75+ years: 38%). The number of patients diagnosed in the 8-year period 1988–96 is similar to the period 1997–05 (438–505 patients); a total of 263 cases were collected in the last 4 years.

The RS analysis by Poisson regression showed that patients <65 years of age had a significant improvement of survival in the periods 1997–05 and 2006–09 compared with the previous years ($P < 0{\cdot}001$). A trend to improvement was also observed from 1997–05 to 2006–09 (relative risk: 0·76, 95% CI 0·50–1·15) but this did not reach statistical significance ($P : 0{\cdot}190$) (Table IV; Fig 2). For patients aged 65–74 years, RS was statistically significantly improved in the period 2006–09 compared with both the years 1988–96 ($P : 0{\cdot}008$) and 1997–05 ($P : 0{\cdot}013$) (Table IV; Fig 2). On the other hand, for patients 75+ years of age RS did not change over time (Table IV; Fig 2). The Cox regression for the OS confirmed the observations of RS, showing a substantial benefit for patients aged <65 years and 65–74 years, with a statistically significant advantage for patients 65–74 years old, after 2006. No advantage in OS was observed for the last cohort of patients (Table III). The trend for calendar years at diagnosis of the RS, with the projection of the linear fit at the period of diagnosis 2006–09 clearly shows that in the age bands <65 years and 75+ years the extrapolated value at 3 years follows the linear trend of the previous six periods (Fig 3). Conversely in the age band 65–74 years, the extrapolated 3-year RS was lower and outside the 95% CI of the observed survival, confirming the improvement of RS in the last 4 years in this group of patients (Fig 3).

Discussion

The increasing knowledge of cancer biology and improvement of translational research resulted in a new era of therapeutic strategies for patients affected by MM. Despite positive advances in cancer treatment, and the improvement of response observed in clinical trials, the impact of novel therapies in an unselected population needs to be confirmed. In the past few years several publications focused on the survival of MM patients, however the data very often referred to clinical trials or single institutions data sets (Kumar *et al*, 2008, 2012; Ludwig *et al*, 2008; Campagnaro *et al*, 2011).

Among the published studies, Mayo Clinic, a tertiary referral centre for MM, observed that the 5-year OS in previously untreated MM patients enrolled in four phase III trials between 1988 and 2006, improved in the years 2001–06, compared with the cohorts 1988–93 and 1994–2000 (Campagnaro *et al*, 2011). They observed that year at diagnosis, and consequently treatment, was not the only factor influencing survival. Age at diagnosis was important, with less benefit observed for patients older than 65 ($P : 0{\cdot}012$).

Another study, published by the same group, which analysed 2981 newly diagnosed MM collected by a single institution in 36 years (from 1971 to 2006), confirmed the amelioration of prognosis over time (Kumar *et al*, 2008). Data showed that, for patients diagnosed after 1996, when HDM/ASCT was introduced into clinical practice, median OS improved from 2·5 to almost 4 years. The improvement was especially significant in the period 2001–06 and it was thought to be related to the introduction of novel therapies. The amelioration of survival was particularly true for patients <65 years of age, concluding that there was a strong impact of both age at diagnosis and year of diagnosis on the survival of MM patients.

Conversely, in the latest study from the Mayo Clinic, over 1056 newly diagnosed myeloma patients followed at a single institution from 2001 to 2010 showed a surprising significant improvement of OS in patients >65 years with only a marginal advantage in younger patients. The multivariate analysis

Table II. Relative survival at 5 years for the periods 1988–96, 1997–05 and 2006–09.

	Periods			
	1988–96	1997–2005	2006–09	Total
Age (years)				
<65	58·1 (48·6–66·6)	73·9 (66·0–80·4)	74·2 (40·5–91·6)	68·8 (63·2–73·7)
65–74	49·9 (40·7–58·8)	46·7 (37·8–55·3)	72·9 (50·3–88·7)	50·2 (44·1–56·2)
75+	29·2 (20·1–39·6)	29·7 (21·6–38·7)	31·4 (14·4–52·6)	29·2 (23·6–35·5)
Sex				
M	42·3 (34·9–49·9)	50·8 (43·4–58·1)	51·5 (29·6–72·0)	48·2 (43·2–53·2)
F	49·5 (41·4–57·4)	49·1 (42·1–56·0)	63·1 (51·8–73·0)	49·8 (44·8–54·6)
Total	45·7 (40·2–51·2)	49·9 (44·8–55·0)	55·7 (41·1–69·0)	49·0 (45·5–52·5)

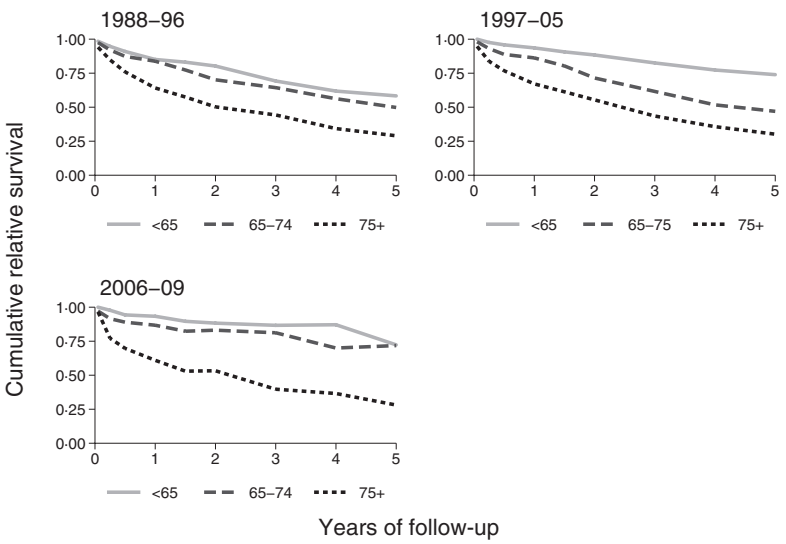

Fig 1. Cumulative Relative Survival of patients in the periods 1988–96, 1997–05 and 2006–09.

Table III. Overall survival at 5 years and Cox proportional-hazard regression.

	Periods			
	1988–96	1997–2006	2006–09*	Total
Age (years)				
<65	55·5 (46·4–63·6)	71·7 (64·0–78·0)	78·3 (56·5–90·0)	66·4 (61·0–71·2)
65–74	43·1 (35·2–50·8)	42·0 (34·0–49·7)	67·8 (49·7–80·6)	44·3 (38·8–49·6)
75+	17·8 (12·3–24·2)	19·0 (13·8–24·8)	20·9 (8·8–36·5)	18·6 (15·0–22·6)
Sex				
M	33·9 (27·9–40·0)	42·3 (36·1–48·4)	47·0 (31·0–61·5)	39·5 (35·4–43·6)
F	42·1 (35·2–48·8)	42·6 (36·5–48·5)	57·5 (47·2–66·5)	43·1 (38·8–47·3)
Total	37·7 (33·1–42·2)	42·5 (38·1–46·7)	50·9 (40·0–60·8)	41·2 (38·3–44·2)

Overall Survival (OS) confirms the observations of the RS. Values given as 5-year OS (95% confidence interval).
*OS a 4·5 years.

showed that the beneficial effect was related to the introduction of novel therapies (Kumar *et al*, 2012).

These three studies, however, refer to selected populations; the first one analysed data from clinical trials and the second and third studies utilized a tertiary, single institution dataset.

Patients enrolled in clinical trials are usually selected, with good performance status and limited comorbidities. On the contrary, patients followed in every day clinical practice are often characterized by a lower than optimal performance status, and sometimes several comorbidities. Based on these

Table IV. Relative survival at 5 years for the age bands <65, 65–74 and 75+ years.

	Multiple poisson regression		
	RR	IC95%	*P*
Age <65 years			
Period			
1997–2005 vs. 1988–96	0·55	0·39–0·77	<0·001
2006–09 vs. 1988–96	0·42	0·27–0·64	<0·001
2006–09 vs. 1997–2005	0·76	0·50–1·14	0·190
Age 65–74 years			
Period			
1997–2005 vs. 1988–96	1·06	0·72–1·57	0·775
2006–09 vs. 1988–96	0·59	0·40–0·87	0·008
2006–09 vs. 1997–2005	0·56	0·36–0·89	0·013
Age 75 + years			
Period			
1997–2005 vs. 1988–96	0·94	0·76–1·16	0·568
2006–09 vs. 1988–96	1·11	0·78–1·56	0·567
2006–09 vs. 1997–2005	1·18	0·85–1·62	0·318

The Relative Survival (RS) percentage (95% confidence interval [CI]) at 5 years and the Multiple Poisson Regression of RS data are shown. In Table II, the data are grouped by age and calendar year at diagnosis. The analysis by year at diagnosis clearly shows an overall progressive benefit of RS for MM patients from the period 1988–96 vs. 1997–05 vs. 2006–09, improving from 45·7% to 49·9% to 55·7%. Survival does not seem to be sex-related.

The sub analysis by age (Table IV) shows that there is no difference in the RS for patients 75 + years. For patients younger than 65 the benefit is particularly evident in the period 1997–2005, when autologous stem cell transplantation was introduced in the clinical practice of Modena, with a less evident and transitory improvement after the introduction of novel agents (73·9 vs. 74·2), confirmed also by the Multiple Poisson Regression (P : 0·190). On the other hand, the era of novel agents significantly improved the survival of the group aged 65-74 years compared with the previous period (RS: 72·9 vs. 46·7), confirmed by the Multiple Poisson Regression (P : 0·013). RR, relative risk.

considerations, data obtained from study populations provide a more general assessment of survival, because they take unhealthy patients into account.

Two Swedish studies (Kristinsson *et al*, 2007; Turesson *et al*, 2010) attempted to analyse survival in the general population.

In a population-based study of patients diagnosed with MM in Malmö, Turesson *et al* (2010) observed that, of 773 patients diagnosed between 1950 and 2005, survival clearly improved after 1960. For patients <65 years of age the benefit increased over the past 50 years, with an expected survival of 56·3 months for patients diagnosed in the years 2000–05 compared with 24·3 months in the years 1960–69, indicating that both the improvement of pharmacology and age at diagnosis influence the prognosis. However, for patients >65 years, no clear benefit was observed after 1960, with a comparable survival expectancy in the 1960s and 2000 (21·2 months in 1960–69 vs. 26·7 in 2000–06). Thalidomide was the only novel agent introduced in the clinical practice in the years 2000–05, administered in 32% of younger patients and 23·5% of the older age group, but data regarding the impact of thalidomide on survival are inconclusive (Turesson *et al*, 2010). The authors also observed a difference of OS in males compared with females, with a shorter survival in men (18·6 vs. 26·3 months) (Turesson *et al*, 2010).

Another Swedish population-based study conducted in 14 381 patients affected by MM diagnosed between 1973 and 2003 reached similar conclusions (Kristinsson *et al*, 2007). In this study, year at diagnosis as well as age and sex, were important factors influencing survival. While the 1-year MM survival improved in all age groups, the 5- and 10-years- RS ratio in the last 30 years improved only in patients <70 and <60 years of age, respectively. Despite the wide dataset, thalidomide was the only novel agent introduced in MM treatment starting from 1998. A total of 1232 patients received thalidomide and the authors proposed a possible

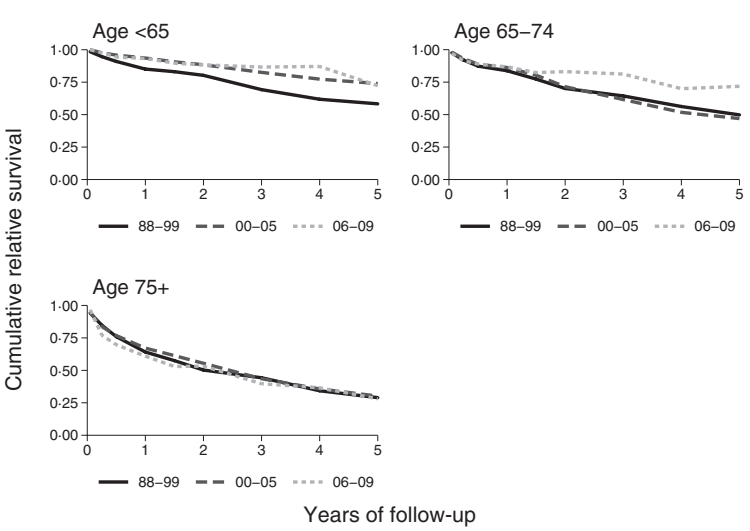

Fig 2. Cumulative Relative Survival of patients affected by multiple myeloma from Modena Cancer Registry by age band.

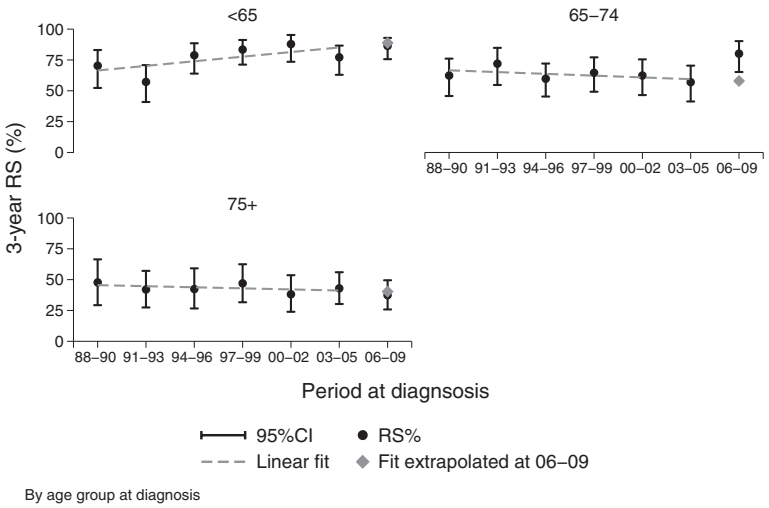

Fig 3. Trend of the 3-years Relative Survival for calendar period at diagnosis stratified by age group at diagnosis. In the age bands <65 and 75+ years the extrapolated relative survival (RS) value at 3-years for the period 2006–09 followed the linear trend of the previous six periods; in band 65–74 years the extrapolated 3-year RS is lower and outside the 95% CI of the observed survival, confirming the improvement of RS in the last 4 years for this group of patients.

benefit on survival, but no major conclusions are possible based on the available data (Kristinsson *et al*, 2007).

In order to evaluate the impact of novel therapeutic approaches in unselected patients affected by MM, we evaluated OS and RS in patients diagnosed in the province of Modena based on MCR dataset. Data were collected between 1989 and 2009 and are representative of a population referring to multiple local institutions, but receiving fairly homogenous treatments. Compared with previously published data, novel treatments administered in MM patients of the province of Modena included thalidomide, bortezomib and lenalidomide, extensively used in our clinical practice after 2006. Novel agents were prescribed in relapsed patients first, and in newly diagnosed patients later; however schedule of administration, doses and clinical details are not available.

Patients diagnosed with MM in the province of Modena are followed by one haematology unit in the hospital affiliated to the University of Modena and Reggio Emilia (and the only transplant unit of the province), and several other hospitals (that are not tertiary referral centres) in the province. The referral of patients to multiple institutions reduces the bias of the site of care. In order to assess the impact of conventional and new therapies on survival, three time frames were identified: 1988–96 (conventional therapy), 1997–05 (after the introduction of HDM/ASCT) and 2006–09 (introduction of thalidomide, bortezomib and lenalidomide in the clinical practice of the province of Modena). Based on age at diagnosis we first analysed two cohorts of patients (<65 and 65+), with 65 years of age representing the cut-off for bone marrow transplant in our practice. This study however did not show a significant difference in survival based on age, and we further separated the second group into cohort of 65–74 years and 75+ years. Although age alone is not a criterion to define patient's fragility, after this sub-analysis, the three curves showed a different trend. We evaluated both OS and RS. Compared with OS, RS excludes the chance of dying from diseases other than cancer, and it is a better indicator of survival in this type of study. Our data showed that for patients <65 years of age, RS improved significantly in the past 15 years, confirming that the introduction of HDM/ASCT into clinical practice represented a turning point in this group of patients. Only a marginal and transitory improvement in these patients was observed in the era of novel agents, confirming that transplantation is currently the best therapeutic option. Future studies will evaluate the benefit of autologous transplant compared with novel agents. More profound is the effect on patients aged 65–74 years. RS improved significantly in this cohort after 1997, particularly after 2006, when novel therapies became available to a larger population. These data support the hypothesis that novel therapies had a major impact on a population that had not benefited from new treatments since the 1960s. Taken together, these results confirm the previous observations that both HDM/ASCT and novel therapies seem to impact the life expectancy of MM patients, outside clinical trials. As previously described, however, no improvement was observed for patients aged 75+ years.

A further analysis of the results by projection of the linear fit at the period of diagnosis 2006–09 confirmed once again that the group aged 65–74 years showed a significant improvement of life expectancy in the past few years, strengthening the observations of the 2012 Mayo Clinic study (Kumar *et al*, 2012).

Compared with the data from two Swedish studies (Kristinsson *et al*, 2007; Turesson *et al*, 2010), our analysis did not show any impact of sex on survival.

The importance of age at diagnosis as a factor influencing survival has been observed in several studies (Ludwig *et al*, 2008; Campagnaro *et al*, 2011; Kumar *et al*, 2012). The analysis of over 10 000 patients diagnosed between 1982 and 2002 and followed in 17 International Working Myeloma Group (IWMG) institutions clearly demonstrated that patients <50 years of age had a significantly prolonged survival compared with older patients (Ludwig *et al*, 2008). The benefit

was partly due to the lower International Staging System of younger patients at diagnosis. A detailed analysis of the median observed survival in different age groups identified a constant decrease from age 40 years to >80 years, dropping dramatically from 6·4 to 2·5 years (Ludwig *et al*, 2008). Over 70% of patients in this study were enrolled in clinical trials.

In conclusion, despite the retrospective nature of our study, the limitation of a small geographical area, and the absence of details of clinical data, such as staging, treatment schedule and supportive care, our study confirms that survival of MM patients has improved in the past few years. We hypothesize that the improvement is related to the introduction of new therapeutic approaches. In particular, the introduction of HDM/ASCT in the 1990s became the major turning point for patients <65 years of age. However the novel data that emerges from this analysis is the observation that the group that seemed to benefit more from the introduction of novel agents in the clinical practice is the subgroup of patients aged 65–74, representing a major therapeutic change. No benefit was observed for subjects aged 75+ years, confirming older age as an important factor influencing survival.

No data was available regarding supportive care in this data set and we cannot exclude that a better prevention and treatment of MM bone disease, anaemia, infections and kidney failure might have influenced survival as well. However we can deduce that all patients, with the same complications and despite age, received the same supportive care in the past 4 years. Nevertheless, an improvement of RS for patients aged 65–74 years was clearly evident, supporting that other factors than supportive care had an impact on the survival.

Future population-based studies are essential to confirm these observations and the development of new therapeutic strategies for elderly patients is needed.

Acknowledgements

The authors thank M. E. Artioli and K. Valla for the collection and management of the data. This work was supported in part by the 'Associazione Angela Serra per la Ricerca sul Cancro'. Samantha Pozzi: performed the research, interpreted the data, wrote the manuscript; Luigi Marcheselli: analysed and interpreted the data; wrote materials and methods, critically revised the manuscript and approved the submitted and final versions; Alessia Bari, Eliana Valentina Liardo, Raffaella Marcheselli, Stefano Luminari, Micol Quaresima, Paola Ferri: critically revised the manuscript and approved the submitted and final versions, Claudia Cirilli: collected the data and approved the submitted and final versions, Massimo Federico supervised the collection and analysis of the data at the Modena Cancer Registry and revised and approved the submitted and final versions, Stefano Sacchi designed the research study, interpreted the data, revised the manuscript with major contributions and approved the submitted and final versions.

References

Campagnaro, E.L., Jacobus, S.J., Uno, H., Oken, M.M., Kyle, R.A., Rajkumar, S.V., Greipp, P.R., Vesole, D.H., Weiss, M., Fonseca, R. & Lazarus, H.M. (2011) Survival outcomes in elderly patients with plasma cell myeloma: the three-decade Eastern Cooperative Oncology Group (ECOG) experience. *Journal of Clinical Oncology*, ASCO Annual Meeting Proceedings (Post-Meeting Edition), **29**, No 15_suppl, 2011: ab. 8021.

Cox, D. (1972) Regression models and life tables. *Journal of the Royal Statistical Society. Series B (Methodological)*, **34**, 187–202.

Dickman, P.W., Sloggett, A., Hills, M. & Hakulinen, T. (2004) Regression models for relative survival. *Statistics in Medicine*, **23**, 51–64.

Ederer, F. & Heise, H. (1959) Instructions to IBM 650 programmers in processing survival computations. Methodological note no. 10. End Results Evaluation Section, National Cancer Institute, Bethesda, MD, USA.

Greenlee, R.T., Murray, T., Bolden, S. & Wingo, P.A. (2000) Cancer statistics, 2000. *CA: A Cancer Journal for Clinician*, **50**, 7–33.

Greipp, P.R., San Miguel, J., Durie, B.G., Crowley, J.J., Barlogie, B., Bladé, J., Boccadoro, M., Child, J.A., Avet-Loiseau, H., Kyle, R.A., Lahuerta, J.J., Ludwig, H., Morgan, G., Powles, R., Shimizu, K., Shustik, C., Sonneveld, P., Tosi, P., Turesson, I. & Westin, J. (2005) International staging system for multiple myeloma. *Journal of Clinical Oncology*, **23**, 3412–3420.

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., Murray, T. & Thun, M.J. (2008) Cancer statistics, 2008. *CA: A Cancer Journal for Clinician*, **58**, 71–96.

Kristinsson, S.Y., Landgren, O., Dickman, P.W., Derolf, Å.R. & Björkholm, M. (2007) Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. *Journal of Clinical Oncology*, **25**, 1993–1999.

Kumar, S.K., Rajkumar, S.V., Dispenzieri, A., Lacy, M.Q., Hayman, S.R., Buadi, F.K., Zeldenrust, S.R., Dingli, D., Russell, S.J., Lust, J.A., Greipp, P.R., Kyle, R.A. & Gertz, M.A. (2008) Improved survival in multiple myeloma and the impact of novel therapies. *Blood*, **111**, 2516–2520.

Kumar, S.K., Dispenzieri, A., Gertz, M.A., Lacy, M.Q., Lust, J.A., Hayman, S.R., Buadi, F.K., Dingli, D., Zeldenrust, S.R., Russell, S., Kapoor, P., Lin, Y., Hwa, L., Larson, D., Colby, C.L., Benson, J.T., Kyle, R.A. & Rajkumar, S.V. (2012) Continued improvement in survival in multiple myeloma and the impact of novel agents. *Blood* (ASH Annual Meeting abstracts), **120**, 3972.

Ludwig, H., Durie, B.M.G., Bolejack, V., Turesson, I., Kyle, R.A., Blade, J., Fonseca, R., Dimopoulos, M., Shimizu, K., San Miguel, J., Westin, J., Harousseau, J.L., Beksac, M., Boccadoro, M., Palumbo, A., Barlogie, B., Shustik, C., Cavo, M., Greipp, P.R., Joshua, D., Attal, M., Sonneveld, P. & Crowley, J. (2008) 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. *Blood*, **111**, 4039–4047.

Palumbo, A. & Anderson, K. (2011) Multiple myeloma. *The New England Journal of Medicine*, **364**, 1046–1060.

Siegel, R., Ward, E., Brawley, O. & Jemal, A. (2011) Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA: A Cancer Journal for Clinician*, **61**, 212–236.

Turesson, I., Velez, R., Kristinsson, S.Y. & Landgren, O. (2010) Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. *Journal of Clinical Oncology*, **10**, 830–834.

Wu, Y.X., Tekkenberg, J.J.M. & Grunkemeier, G.L. (2008) Measuring follow-up completeness. *The Annals of Thoracic Surgery*, **85**, 1155–1157.