The burden of multiple myeloma: assessment on occurrence, outcomes and cost using a retrospective longitudinal study based on administrative claims database

Simona de Portu[1], Renato Fanin[2], Francesca Patriarca[2], Andrea Morsanutto[3], Francesca Tosolini[3], Renato Esti[3], Lorenzo G. Mantovani[1]

[1]CIRFF, Center of Pharmacoeconomics, Federico II University of Naples, Naples, Italy; [2]Division of Haematology, Department of Clinical and Morphological Researches, University of Udine, Udine, Italy; [3]Friuli Venezia Giulia Regional Health Authority, Trieste, Italy

Correspondence to: Lorenzo G. Mantovani, CIRFF/Center of Pharmacoeconomics, Faculty of Pharmacy, University of Naples, Federico II. Via Montesano, 49 80131 Naples (Italy). E-mail: mantovani@unina.it.

Abstract

Objective: Multiple myeloma (MM) is a malignancy of plasma cells that results in an overproduction of light and heavy chain monoclonal immunoglobulins. Multiple myeloma imposes a significant economic and humanistic burden on patients and society. The present study is aimed at assessing the burden of multiple myeloma in both epidemiologic and economic terms.

Methods: A retrospective, naturalistic longitudinal study on the occurrence, outcome and cost of multiple myeloma using an administrative database, was performed. We selected residents of a North-eastern Region of Italy, who had their first hospital admission for multiple myeloma during the period 2001-2005. This group was followed up until 31-12-2006, death or transfers to other regional health services. Direct medical costs were quantified within the perspective of the Regional Health Service.

Results: During the period 2001-2005, out of a population if 1.2 million inhabitants, we observed 517 incidents of patients diagnosed with MM (52% female). During the period of observation, 364 (70.4%) subjects died. Total health care costs per patient over the maximum of follow-up were estimated to be 76,630 Euro for subjects younger than 70 years old and 22,892 Euro in the older group.

Conclusions: Multiple myeloma imposes a significant epidemiological and economic burden on the healthcare system.

Key words: administrative database, cost, incidence, multiple myeloma

Introduction

Multiple myeloma (MM) is a malignancy of plasma cells that results in an overproduction of light and heavy chain monoclonal immunoglobulins. Tumour growth leads to bone marrow failure and complications such as renal insufficiency and bacterial infections. Multiple myeloma causes significant skeletal morbidity (e.g., pain and pathologic fractures) resulting from osteolytic lesions, and the associated medical costs can be considerable. The patients also experience a marked reduction of health-related quality of life (HR-QOL), with reduced physical functioning, fatigue and pain being the most distressing problems [1]. The pathogenesis is poorly understood, but there are emerging insights that may eventually link the clinical entity to its etiology [2]. The American Cancer Society estimated that about 19,900 new cases of MM would be diagnosed during 2007 in US, and about 10,790 of these were expected to die of the disease [3].

Internationally, MM constitutes approximately 1% of all cancers worldwide, with approximately 86,000 new cases per year. Incidence rates vary from 0.4 to 5 per 100,000 with a slight male preponderance [4].

Multiple myeloma is rarely diagnosed prior to age 40 [2,4], after which the incidence increases rapidly until age 84 and then declines. The incidence is high in North America, Australia, New Zealand, Northern Europe, and Western Europe compared with Asian countries. The five-year survival rate for patients with myeloma was 15% to 20% [4]. Over the past 5 years, significant progress has been made in the diagnosis and assessment of patients with MM. For the first time in decades, major therapeutic advances have been implemented in the treatment of MM patients. These include 2 new

classes of agents: immunomodulatory drugs and proteosome inhibitors. In addition, clinical trials have solidified the role of hematopoietic stem cell transplant and established the benefits of post-transplant maintenance therapy. Finally, a number of new agents are in development that specifically target the myeloma cells and/or the bone marrow microenvironment [5]. Drugs, such as thalidomide, lenalidomide, and bortezomib, are potentially changing the therapeutic paradigm of multiple myeloma and offer hope for better outcomes [6-13]. These advances have resulted in expanded treatment options, prolonged disease control and survival, and improved quality of life for patients with MM [5]. Since there is a lack of information worldwide on the burden caused by MM, the present study is aimed at evaluating the frequency of its occurrence and related outcome, and cost of care of MM simultaneously, thus providing empirical evidence about the real burden of MM in Italy and in particular in the Friuli Venezia Giulia (FVG) Region.

Methods

To pursue the aim of the study, we carried out a retrospective, longitudinal, naturalistic study based on claims of individuals enrolled in the administrative database of Friuli Venezia Giulia region of Italy. The Regional Health Authority (RHA) is in charge of the universal healthcare coverage of all its regional residents, with approximately 1.2 million stable inhabitants, located in north-eastern Italy. The area is characterised by modest migration flows, so the FVG RHA archives have been used in the last two decades for other epidemiologic and burden of disease research. All calculations about the incidence of the disease were made under the hypothesis of a stable population. The analysis was carried out from the perspective of the Regional Health Service. For the purpose of this study, hospital admissions, outpatient care, drug prescriptions and mortality databases were accessed, and patients were identified and followed longitudinally by means of an alphanumeric code that univocally identified each enrolee of the RHA. The source population for this study were residents of the FVG region between 1996 and 2006. The population included in the study comprised of people who had a first hospital admission event with diagnosis of MM (ICD9 code 203.00) occurring during the period between 01/01/2001 and 31/12/2005. Patients with a code number 203.00 reported in hospital discharge forms (SDO) were also considered, both in the case of full admissions or for day care admissions documented during the study period. The date of MM diagnosis was considered as the index date, i.e. the date of inclusion into the study population. In order to be able to identify incident cases, to follow them up, and to minimize risk of overlapping oncological diagnoses (particularly metastases), individuals with a diagnosis of cancer (ICD9 code 140-230) in the years from 1996 to 2000, and patients coming from other Regions, were excluded from our analysis.

Selected patients were followed-up until the 31st december 2006, death, or withdrawal from the RHA (i.e. transfer out of the Region), whichever came first. Therefore the individual length of follow up was variable. Demographic characteristics (age and gender) were collected at baseline (on admission), while information about vital status, outpatient care, drug prescription and hospital admission were collected during the follow-up period. Diagnosis related group (DRG) tariffs [14] were applied to estimate the cost of hospitalizations, and drug prescriptions information were obtained from the pharmaceutical database that includes every prescription dispensed to outpatients by the community pharmacies. Drug therapies were quantified using market prices reported by the Italian National Therapeutic Formulary [15]. The Outpatient care database, including visits, diagnostic and laboratory tests, was used to quantify resource absorption, while costs were calculated by means of Ambulatory tariffs [16]. The cumulative incidence was calculated as the ratio of incidence cases to the at-risk population in 2001. All costs are expressed in Euros referred to 2006 tariffs and have been calculated as the sum of all claims related to MM incident subjects recorded after the index date. Costs are expressed as Euros per patient and are further described as costs within the first year (i.e 365 days from the index date) and as total costs (i.e. for the entire follow-up period), because these can be used for short and long term planning needs of Health Authorities. The research was approved by the relevant institutional review boards. Estimates of central tendency were expressed by using means and frequencies, and standard deviation was used as a measure of dispersion

Kaplan-Meier estimates of survival in patients over 70 years of age at diagnosis or less than 70 years were compared using a log-rank test. The 70 years of age cut off was chosen because it is considered normally as a discriminator for being a candidate for bone marrow transplant. Univariate and multivariate analyses of survival using the Cox proportional hazards method were performed to obtain the hazard ratios for

death, and associated 95 percent confidence intervals (95% CI) for the comparison between younger and older patients. Mean cost differences were subsequently estimated fitting a linear least squares regression model adjusting for sex. Point and interval estimates of differences between patients over 70 years of age at diagnosis and those under 70 were assessed resorting to a bootstrap technique with 5,000 samples. All analyses were performed using SPSS versions 15.0 software (SPSS, Chicago, IL).

Results

During the study period (Jan 2001-Dec 2005), 517 patients were diagnosed with MM and a mean age of 73.2 years was seen (52% female). 65% of the sample had an age at diagnosis of more than 70 years old (Table 1). The crude incidence of MM is 8.61 per 100,000 persons . The incidence proportion in different age strata is showed in Figure 1. During the observation period, 364 subjects died (70.4%), 90 subjects in the younger group (49%) and 274 (82%) subjects in older one (70 years old and over), with a mean survival of 557 days. The risk of death was significantly higher among older patients (70 years old and over) with a mean survival of about 13 months, as inferred from the log rank test p value < 0.05 (Figure 2) Compared with younger patients, older MM patients (70 years and over) had an increased risk of death (hazard ratio 2.69, 95% CI 2.11 to 3.42; P<0.0001). After adjustment for sex, the hazard ratio associated with age was not significantly affected by the baseline characteristic examined. Total healthcare costs per patient over the maximum follow-up period were estimated to be 78,020 Euros for the younger group and 23,096 Euro for the older one (Table 2) with a mean difference of 54,932 Euro after adjusting for sex. Inpatient costs for MM patients less than 70 years of age at diagnosis were 64,662 Euro (83% of total cost) and 18,020 Euro (78%) for the older group. Ambulatory and diagnostic costs per patient were 6,915 Euro (9%) and 2,814 Euro (12%) for younger and older patients, respectively.

The cost per patient related to the first year after diagnosis was 42,948 in the under 70 group and 14,669 Euro in the over 70's, respectively, with a mean difference of 28,128 Euro after adjusting for sex (Table 3). The vast majority of the total costs estimated, either in the first year after diagnosis and during the entire follow-up, can be attributed to hospital care (Tables 2 and 3).

Conclusions

This is the first study assessing the occurrence of MM, it's cost and it's outcomes from the paying service user's perspective in Italy, and one of the few ever performed. It is, therefore, difficult in the absence of any comparative data to place our results in the light of other settings. MM is a disease more frequently seen in older age, particularly from the 8th decade of life onwards, with high overall mortality. Regarding mortality, more than 2/3 of patients died during the follow-up period. However, as expected, mortality was far greater in individuals older that 70 years of age compared to younger patients. In a relatively recent report from Medical Research Council trials [17], early mortality (60 days) is reported to be higher in older compared to younger patients, confirming age to be an important predictor of prognosis. Our data showed that 60 day mortality was 4.4% in individuals younger than 70 years and 22.9% in individuals older than 70 (data not shown). As far as costs are concerned, the overall cost per patient was estimated to be approximately 25,000 Euro during the first year and higher than 42,000 Euro during the entire follow-up period.

Table 1. Population characteristics, stratified according to age: <70 years vs >70 years.

Variable	*< 70 years*	*≥ 70 years*
N=517	182 (35.2%)	335 (64.8%)
Age (years)	60.61	80.11
Sex *Male* *Female*	 98 (53.8%) 84 (46.2%)	 150 (44.8%) 185 (55.2%)
Length of follow-up (days)	931.07	523.82
Mortality	0.49	0.82

Figure 1. Cumulative incidence of MM (new cases per 100,000 persons) in different age strata.

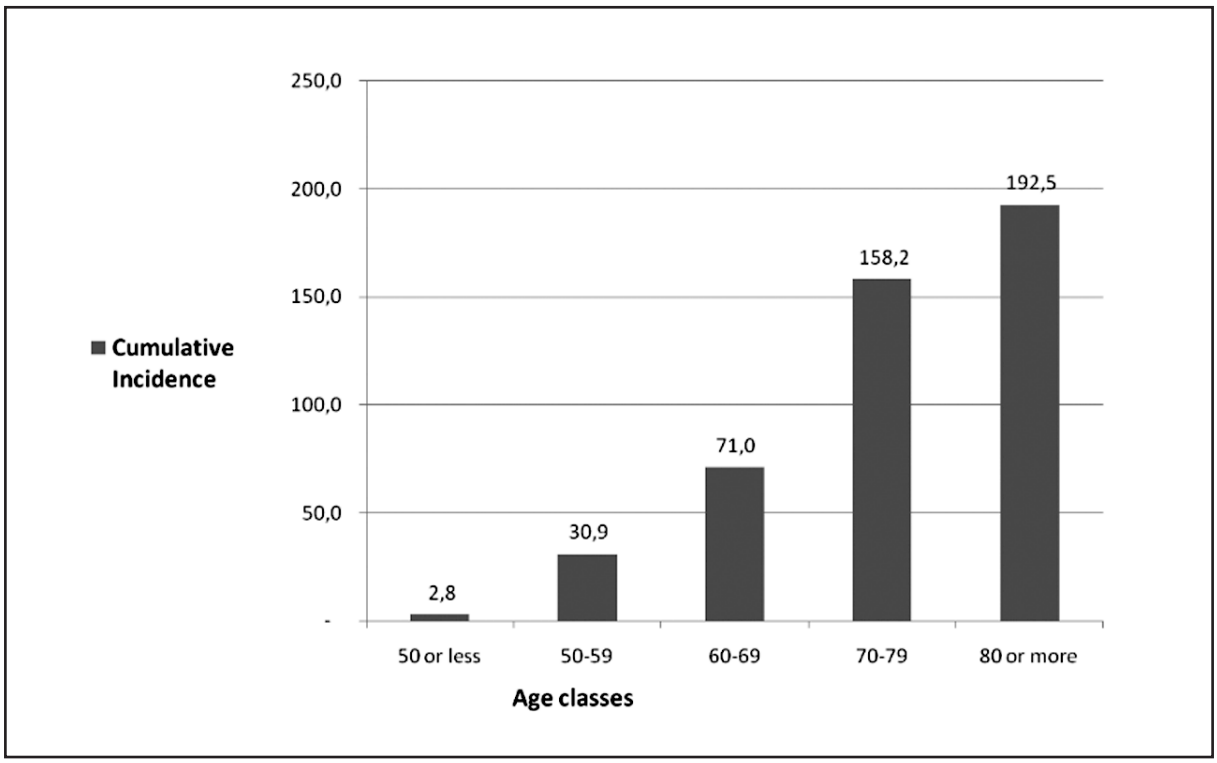
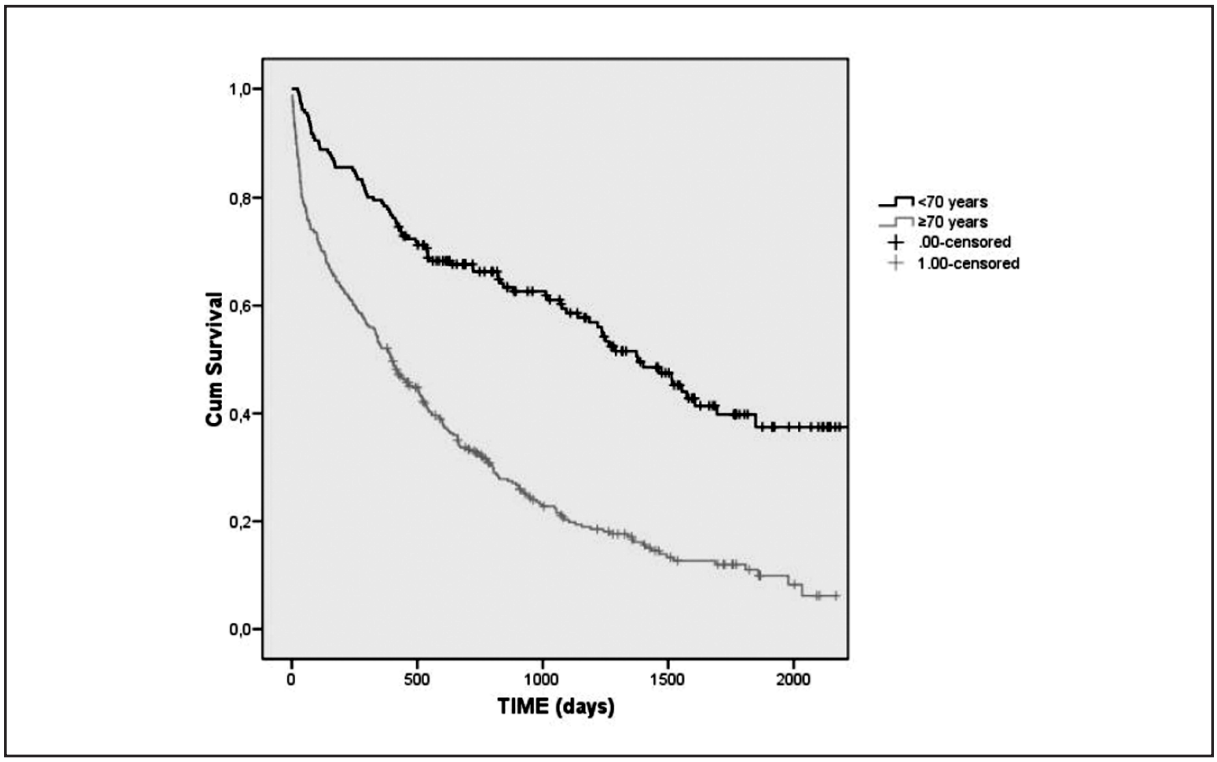


Figure 2. Kaplan Meier survival curves of individuals aged <70 years vs 70 years or older.



The vast majority (more than ¾) of the total costs are attributable to hospital care, accounting for approximately 90% of costs in the first year after diagnosis. Results from our study showed that, due to the large number of hospitalizations and the high mortality rate, the epidemiological and socioeconomic burden of MM to the healthcare system and to society is high. The overall cost of MM is substantial, particularly in the first year after diagnosis and principally due to hospital care. The natural history of the disease requires a great absorption of resources in the early phases

Table 2. Cost per patient during entire follow-up period expressed in Euro.

Variable	*< 70 years*	*≥ 70 years*	*Difference (95% CI)*	*Difference (95% CI)**
Cost of hospitalization	64,662.29	18,020.09	-46,642.20 (-53,849.29/-39,435.12)	-46,637.87 (-53,963.79/-39,311.94)
Cost of drugs	6,053.43	2,057.52	-3,995.91 (-5,337.29/-2,654.53)	-4,107.65 (-5,483.67/-2,731.63)
Cost for outpatient care	6,915.18	2,814.68	-4,100.50 (-6,032.54/-2,168.47)	-4,187.21 (-6,060.45/-2,313.97)
Total health care cost	76,630.90	22,892.29	-54,738.62 (-63,373.76/-46,103.48)	-54,932.7 (-63,610.54/-46,254.91)
* adjusted for sex				

Table 3. Cost per patient in the first year of follow-up expressed in Euro.

Variabile	*< 70 years*	*≥ 70 years*	*Difference (95% CI)*	*Difference (95% CI)**
Cost of hospitalization	38,060.33	12,670.33	-25,389.99 (-29,893.86/-20,886.13)	-25,165.40 (-29,757.93/-20,572.87)
Cost of drugs	2,694.99	1,137.41	-1,557.58 (-2,169.08/-946.09)	-1,580.43 (-2,193.63/-967.24)
Cost for outpatient care	2,193.63	861.46	-1,332.17 (-1,844.93/-819.41)	-1,382.43 (-1,904.18/-860.69)
Total health care cost	42,948.94	14,669.19	-28,279.76 (-33,188.10/-23,371.41)	-28,128.27 (-33,047.57/-23,208.97)

after diagnosis and in the later stages of the disease. Despite the evidence we present, which is based on more than 5 years observation pooled from a source population composed of 1.2 million subjects in the FVG RHA database, which had a study sample of more than 500 subjects and which reported measurements of real practice, actual resource absorption and costs directly borne by the third party payer, our study has potential limitations. Firstly, direct costs, other than those for hospitalization, drug therapy and diagnostic test and outpatients care, could not be measured as they are not reimbursed by the third party payer. This is likely to cause an underestimate of the costs, though probably marginal respect to the total burden of care for MM, as costs associated to nursing or other resources for personal care were not available. A second limit is the absence of information about indirect costs, i.e. productivity loss, as well as intangible consequences, such as health related quality of life impairment. This is likely again to lead to an underestimate of the total burden. Anyway, the impact of indirect costs on society might be of modest economic value, as indirect costs are expected to represent around 10% of total cost [17] and given that the age of onset of MM is high and most patients are likely to be already retired when the disease is diagnosed. Although conservative, the results of this study show that MM has a considerable economic impact on the Region. The present analysis refers to the period before the pharmaceutical drugs

bortezomib and lenalidomide were introduced, and before thalidomide was formally approved by regulatory authorities into the therapeutic armamentarium. In fact, the introduction of thalidomide represents a major milestone in the treatment of myeloma, and the subsequent availability of its analog, lenalidomide, and the proteasome inhibitor bortezomib, have expanded the therapeutic options for myeloma [6,7,12, 18-20]. With the introduction of these much more effective, but much more costly therapeutic agents, the structure and the level of cost and outcomes may change in the future. This cohort of patients will be available for comparisons of cost estimates and outcomes after new therapies are introduced, and will, thus, be useful to gauge whether these new therapies might produce a cost effective impact. Evidence from this study will be potentially beneficial to estimate how preventive strategies stack up against established outcomes, as well as if new therapies which have recently become available have a real economic benefit in terms of the real costs of treatment.

References

1) Wisløff F, Eika S, Hippe E et al. Measurement of health-related quality of life in multiple myeloma. Br J Haematol 1996;92:604-13.

2) Alexander DD, Mink PJ, Adami H et al. Multiple myeloma: A review of the epidemiologic literature. Int J Cancer 2007;120:40–61.

3) Jemal A, Siegel R, Ward E et al. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43–66.

4) Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.

5) Katze JA, Hari P, Vesole DH. Multiple Myeloma: Charging Toward a Bright Future. CA Cancer J Clin 2007;57:301–18.

6) Singhal S, Mehta J, Desikan R et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999;341:1565-71.

7) Richardson PG, Sonneveld P, Schuster MW et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487-98.

8) Richardson PG, Barlogie B, Berenson J et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348:2609-17.

9) Dimopoulos MA, Spencer A, Attal M et al. Study of lenalidomide plus dexamethasone versus dexamethasone alone in relapsed or refractory multiple myeloma (MM): Results of a phase 3 study (MM-010). Blood 2005;106:230a(abstr 6).

10) Weber D, Chen C, Niesvizky R et al. Lenalidomide plus high-dose dexamethasone provides improved overall survival compared to high-dose dexamethasone alone for relapsed or refractory multiple myeloma (MM): Results of a North American phase III study (MM-009). J Clin Oncol 2006;24(suppl):427s (abstr 7521).

11) Palumbo A, Bringhen S, Caravita T et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: Randomised controlled trial. Lancet 2006;367:825-31.

12) Rajkumar SV, Hayman SR, Lacy MQ et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood 2005;106:4050-3.

13) Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med 2004;351:1860-73.

14) Ministry of Health. Decree 14th December 1994. "Tariffe delle prestazioni di assistenza ospedaliera". Suppl. to "Gazzetta Ufficiale" n. 209, 8th September 1997

15) Italian National Therapeutic Formulary, 2000 and subsequently updating.

16) DGR n. 1276, 2 may 1997 and subsequently updating.

17) Auguston BM, Begum G, Dunn JA et al. Early Mortality After Diagnosis of Multiple Myeloma: Analysis of Patients Entered Onto the United Kingdom Medical Research Council Trials Between 1980 and 2002—Medical Research Council Adult Leukaemia Working Party. J Clin Oncol 2005;23:9219-26.

18) Rajkumar SV, Blood E, Vesole D et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2006;24:431-6.

19) Kumar S, Anderson KC. Drug insight: thalidomide as a treatment for multiple myeloma. Nat Clin Pract Oncol 2005;2:262-70.

20) Kumar SK, Rajkumar V, Dispensieri A et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008;111:2516-20.