VOLUME-7, ISSUE-2, FEBRUARY-2018 • PRINT ISSN No 2277 - 8160

Original Research Paper

Hematology

MORTALITY OF ADULT PATIENTS WITH MULTIPLE MYELOMA FROM THE BRAZILIAN NATIONAL HEALTH SYSTEM OVER THE PAST 20 YEARS

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ABSTRACT

Objective. To evaluate trends in mortality among adults with multiple myeloma (MM) from the Brazilian National Health System (named SUS).

Methods. Data from DATASUS database provided the number of deaths caused by MM and the number of inhabitants/year in Brazil from 1996 to 2015. Registries were categorized into three age ranges (over 20 years, 20-59 and over 60 years) for an estimation of the annual percent change (APC) for age-adjusted mortality rates using the Joinpoint regression analysis model.

Results. A significant annual increase of 2.5% (95% CI +2.0 to +3.0%) for the age-adjusted mortality rates was observed in the entire sample (over 20 years). Upward trends were also demonstrated for the groups 20-59 (APC +1.3%, 95% CI +0.6 to +2.1%) and over 60 years (APC +3.4%, 95% CI +2.8 to +4.0%).

Conclusion. Upward trends in mortality were observed among MM patients from the SUS over the past 20 years.

KEYWORDS : Multiple myeloma, mortality, survival

Introduction

Multiple myeloma (MM) is a neoplasm of plasma cells that affects 1 to 5 per 100,000 individuals each year worldwide with a higher incidence in the West and accounts for 10% of all hematologic malignancies.[1-3] The MM incidence is expected to increase due to ageing populations and although such disease does not yet have a cure, better diagnosis and new treatments have improved the standard of living for myeloma patients in addition to extending the life expectancy substantially.[4-9]

The assessment of mortality data is a useful tool for monitoring outcomes in patients with hematologic malignancies, particularly in those countries where the survival estimates from cancer registries are not broadly available.[10,11] In Brazil, the National Health Service (named SUS) covers all citizens and roughly only 25% of the population has private health insurance.[12] Despite the attempt of this system to provide full and comprehensive care to the citizens,[13] there are insufficient data to make discussions regarding the death rates from MM.

We *hypothesize* that such data might be relevant to the strategic planning of health managers enabling the implementation of measures to improve services that treat patients with MM. Therefore, the aim of the present study was to perform exploratory data analyses of mortality trends in adult patients with MM from the SUS over the past 20 years.

Methods

This study was carried out by the Centro de Hematologia do Vale (CHV). The CHV consists of medical oncohematological representatives of the following services: Pio XII Hospital in São José dos Campos and Regional Hospital of the Vale do Paraíba, located in the city of Taubaté. These non-teaching hospitals are referral centers from the Regional Health Division XVII, composed of 39 municipalities in the Vale do Paraíba and have treated patients with hematologic malignancies under the SUS since early 1999.

Data from DATASUS available on the Brazilian Ministry of Health website[14] (Health Information, TABNET, statistic data) were considered for inclusion in the analysis. Registries from the five regions of Brazil provided the number of deaths per year caused by MM categorized as C90 according to the International Classification of Diseases 10 (ICD-10) from 1996 to 2015. To obtain a set of data with adequately specified characteristics, registries were grouped according to seven age ranges (in year): 20-29, 30-39, 40-49, 50-59, 60-69, 70-79 and more than 80. Registries from DATASUS also provided the number resident inhabitants per year according to the above-mentioned ranges of age (Health Information, TABNET, demographic and socioeconomic data);[14] thus the death rates per 100,000 inhabitants named crude mortality rate (CMR) were calculated. These age groups were compared using the one way ANOVA Kruskal-Wallis test with Dunn's multiple comparisons test. The Spearman correlation coefficient r was used to measure the strength of association between CMR and time (years of the study) according to the age groups. Overall, p values less than 0.05 were considered statistically significant. We also estimated the average annual percent change (APC) of the age-adjusted mortality rates (APC based on rates that were age-adjusted for the 2000 standard million population) by fitting a straight-line regression to the natural logarithm of the rates, with calendar year used as a regressor variable in a joinpoint regression analysis[15] using the Joinpoint Regression Program (version 4.0.4).[16] The APC were considered significant when the 95% confidence intervals (95% CI) excluded zero ($p < 0.05$).

Results

The CMR rose across the highest age groups with similar values being found among patients aged 60-69, 70-79 and over 80 years (Figure 1).

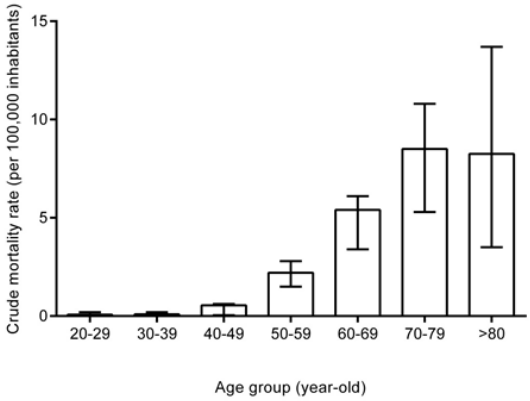

Figure 1. Estimated crude mortality rate (per 100,000 inhabitants) according to age ranges. Data were expressed as mean ± standard deviation (error bars). Similar values were observed for the groups 60-69, 70-79 and over 80 years (Kruskal–Wallis test with Dunn's multiple comparisons test).

Stronger positive correlations between CMR and time were also found among these groups (Table 1).

Table 1. Correlation between crude mortality rate and time (from 1996 to 2015) according to age groups (Spearman r correlation test).

Age group (year-old)	r	95% CI	*p* value (two-tailed)	*p* value summary
20-29	0.0262	-0.4581 to 0.4986	0.9176	Non significant
30-39	0.3524	-0.1518 to 0.7111	0.1515	Non significant
40-49	-0.1611	-0.5939 to 0.3440	0.5231	Non significant
50-59	0.2588	-0.2509 to 0.6561	0.2997	Non significant
60-69	0.9663	0.9073 to 0.9880	<0.0001	Significant
70-79	0.8750	0.6820 to 0.9541	<0.0001	Significant
Over 80	0.9933	0.9811 to 0.9976	<0.0001	Significant

Based on these initial findings, data were categorized into three age groups for the APC estimation of the age-adjustment mortality rates, over 20 years, 20-59 and over 60 years, respectively. The entire sample (over 20 years) showed a significant annual increase of 2.5% in the age-adjusted mortality rates across the 20-year period studied (Figure 2). Upward trends were also demonstrated for the groups 20-59 and over 60 years (Table 2). According to Brazil´s regions all of them showed significant annual increase of the mortality rates in the same period (Table 3).

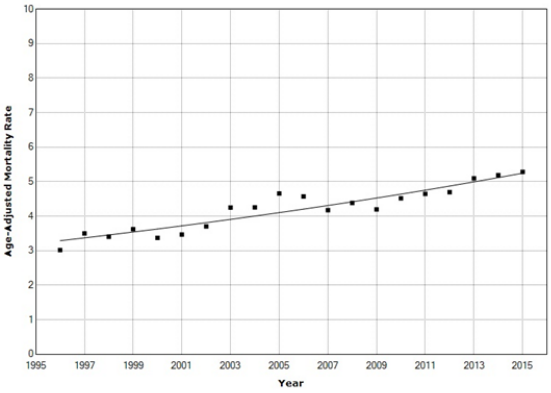

Figure 2. Trends in age-adjusted mortality rate for MM patients aged over 20 years from 1996 to 2015 (average APC +2.5%, 95% CI +2.0 to +3.0%, p<0.05).

Table 2. Average APC estimates of the age-adjusted mortality rates among patients with MM according to age group in Brazil, from 1996 to 2015. *p<0.05

Age group (year-old)	Average APC (%)	95% CI
Over 20	+2.5*	+2.0 to +3.0
20 to 59	+1.3*	+0.6 to +2.1
Over 60	+3.4*	+2.8 to +4.0

Table 3. Average APC estimates of the age-adjusted mortality rates among patients aged over 20 years with MM according to regions in Brazil, from 1996 to 2015. *p<0.05

Region	Average APC (%)	95% CI
North	+5.0*	+2.4 to +7.7
Northeast	+5.7*	+4.8 to +6.6
Midwest	+2.6*	+1.2 to +4.1
Southeast	+1.4*	+0.7 to +2.0
South	+1.5*	+0.7 to +2.3

Discussion

MM incidence increases with age and outcomes are age and performance status dependent. Older patients have more comorbidities and higher incidence of poor prognostic factors such as kidney damage and dys*function; these* statements may explain, at least in part, the increased CMR observed in the elderly groups. In agreement, Schaapveld M et al.[17] studied the effect of the period of diagnosis, age, gender, Salmon-Durie stage, trial participation and treatments on relative survival of 4,985 patients diagnosed with MM in the Northern part of the Netherlands between 1989 and 2005 and demonstrated that relative survival decreased significantly with age and advanced stage. On the other hand, we observed that the CMR rose across time in older patients and this scenario is difficult to explain. Considering that SUS covers all citizens and only 25% of the population has private health insurance[12] one may argue that the number of MM cases increased across the time and consequently more deaths were recorded. However, if this hypothesis is true it is reasonable to presume that the SUS has failed in delivering earlier diagnosis and more accurate treatments since such interventions are *most* likely to impact on reducing *mortality. In this context,* Kumar SK et al.[18] studied the impact of the introduction of new treatments on the mortality and outcomes of 1,038 patients with MM between 2001 and 2010 and demonstrated improved survival and reduced early mortality rates in the entire sample including older patients.

Our analyses also demonstrated an upward trend in age-adjusted mortality rates, which averaged 2.5% per annum since 1996 in the entire sample. With regard to outcomes, studies have been reported in opposite directions; *even in different regions of the Europe and the Northern America where the MM incidences are higher than Brazil,*[19] *the respective mortality has decreased over time. The* EUROCARE-5 Working Group aimed to estimate time trends in a population-based survival for 11 lymphoid and myeloid malignancies in 20 European countries; the authors investigated 560,444 cases from 1997 to 2008 and observed survival increased for most malignancies including those patients with MM.[20] Renshaw C et al.[21] investigated trends in the epidemiology and survival of 15,010 patients diagnosed with MM between 1985 and 2004 extracted from the Thames Cancer Registry database in South East England and demonstrated an improved survival for patients of all ages and such finding were likely to reflect increased detection, earlier diagnosis and the introduction of new treatments. Kaya et al.[22] studied 40,294 MM patients obtained from the Surveillance, Epidemiology, and End Results Program (SEER) of the United States National Cancer Institute in the years from 1973 to 2003; as the largest population analysis to date, this study revealed a statistically significant improvement in overall survival for MM patients who were treated in more recent decades, even before the availability of novel agents. In an elegant study using data from the SEER, Pulte D et al.[23] assessed trends in survival and disease-related mortality for patients with MM by ethnic group, including non-Hispanic whites, African-Americans, Hispanics and people of Asian and Pacific Islander descent from 1998-2001 to 2006-2009. Interestingly, the authors found that survival increased greatly for non-Hispanic whites between 1998-2001 and 2006-2009 and smaller increases were observed for people of other ethnic groups; persistent excess mortality was seen for African-Americans and Hispanic suggesting that ethnic minorities may not have benefited from newer treatments.

In comparison, among the Brazilian patients covered by the SUS, there is still biased allocation of resources, underinvestment in equipment and infrastructure and inequities in cancer care among the different regions of Brazil. In addition, there is no currently government approval for the use of lenalidomide and proteasome inhibitors for MM patients and it is reasonable to consider that these aspects reflected in our findings. Moreover, some institutions have provided all aspects of health care to specific populations while excluding others which consequently worsen the mortality. Taken together, all these facts may explain the higher mortality rates observed in people from regions North, Northeast and Midwest than those living in non-poor areas of Brazil such as southwest and south regions respectively (Table 3).

As demonstrated in another study by our team,[24] an important limitation in this kind of analysis regards data quality. We believe that data extrapolated from the DATASUS database are useful for clinical and epidemiological studies, however erroneous ICD codes registration results in misclassification and could be responsible for the differences in mortality rates observed in our series. It should be

also stressed that in many areas of Brazil, access to timely cancer care is impaired by inadequate health system infrastructure, especially in low-income and geographically isolated populations and these cases are more likely to be unreported than the cases treated in hospitals. Furthermore, the rate of mortality from a disease is a kind of measure of disease burden, as the number of patients who survive long enough to die from another cause or who are cured of the disease influences it. Finally, the present study was based on a cross-sectional framework and registries did not provide whether deaths occurred during or after specific treatments, and we therefore, could not establish a cause effect relationship. Thus we did exploratory data analyses that report the mortality rates and the results gained over a period of time according to a specific diagnosis.

Conclusion

In conclusion, despite the above-mentioned limitations, our data suggested a significant upward trend in mortality among adult MM patients from the SUS over the past 20 years. We believe that our data could be used to fuel a variety of efforts to improve the quality of care system in Brazil and to influence g*overnment decisions, including the introduction of newer treatments for MM patients.*

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