ARTÍCULO ORIGINAL

Clinical characterization and survival of patients with multiple myeloma in a state of northeast brazilian

Caracterización clínica y supervivencia de pacientes con múltiple mieloma en un estado del noreste Brasil

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ABSTRACT

Introduction: The annual prevalence of Multiple Myeloma in patients aged between 65 and 74 years old is 31 cases for every 100 000 people and increases to 46 cases per 100 000 people in patients older than 75 years old.
Objectives: To clinically characterize patients with multiple myeloma treated at a referral center in the state of Rio Grande do Norte, Brazil, and to estimate their survival.
Methods: Retrospective cohort study. For data collection, secondary sources listed in the cadastral database and complementation with data records was used. The descriptive analysis was performed by using the Epi Info program, version 3.5.2 and the survival analysis used Statistic Package for Social Sciences (SPSS) software version 22.
Results: Out of the 39 patients studied, 17 (43.6%) were male, and 22 (56.4%) were female, with an average age of 66.3 years old. The main medication therapeutic regimen was the combination of Cyclophosphamide, Thalidomide, and Dexamethasone (CTD), as the most medical prescription used in 63.6% of cases. Only 38.5% had other comorbidities and 46.2% of patients developed plasmacytoma. In the International Staging System (ISS), stage III prevailed with 30.8% among the evaluated patients.

The cumulative probability of global survival rate showed a disease with a survival rate of 50% of the sample in about 36 months (three years) after diagnosis is confirmed.

Keywords: multiple myeloma; plasmacytoma; bone marrow; epidemiology.

RESUMEN

Introducción: la prevalencia anual de mieloma múltiple en pacientes entre 65 y 74 años de edad es de 31 casos por cada 100 000 personas y aumenta a 46 casos por 100 000 personas en pacientes mayores de 75 años.
Objetivos: caracterizar clínicamente a los pacientes con mieloma múltiple tratados en un centro de referencia en el estado de Rio Grande do Norte, Brasil, y estimar su supervivencia.
Métodos: estudio de cohorte, retrospectivo. Para la recopilación de datos, se utilizaron fuentes secundarias de la base de datos catastral y complementación con registros de datos. El análisis descriptivo se realizó mediante el programa Epi Info, versión 3.5.2 y el análisis de supervivencia del software estadístico SPSS 22.
Resultados: de los 39 pacientes estudiados, 17 (43,6 %) eran varones y 22 (56,4 %), mujeres; con una edad promedio de 66,3 años. El principal régimen terapéutico de medicación fue la combinación de ciclofosfamida, talidomida y dexametasona (CTD), como la prescripción médica más utilizada en el 63,6 % de los casos. Solo el 38,5 % tenía otras comorbilidades y el 46,2 % de los pacientes desarrolló plasmocitoma. En el *International Staging System* (ISS), prevaleció la etapa III (30,8 % de los pacientes evaluados). La probabilidad acumulada de supervivencia global mostró una enfermedad con una tasa de supervivencia del 50 % de la muestra en aproximadamente 36 meses (tres años) después de que se confirmó el diagnóstico.

Palabras clave: mieloma múltiple; plasmocitoma; médula ósea; epidemiología.

INTRODUCTION

Multiple Myeloma (MM) is a monoclonal differentiated B cells tumor that synthesizes a monoclonal protein, and it is reproduced predominantly in the bone marrow. With a consequent production of defective monoclonal immunoglobulins associated with multiple organ dysfunctions, it is 1% of all malignancies in general and 10% of hematological cancer [1-3].

The annual prevalence of MM in patients aged between 65 and 74 years old is 31 cases for every 100,000 people and increases to 46 cases per 100,000 people in patients older than 75 years old[4]. As to gender, this type of cancer is more common in the male population and despite being present in all ethnic groups, it is higher in black population[5].

The MM is difficult to diagnose, and it can present non-specific or vague symptoms. Therefore, when there is suspicion of myeloma, many investigations must be conducted, including the anamnesis with an approach to family history and physical examination aided by the general laboratory tests of hematological order, radiological evaluation of the skeleton, among others. Immunofixation is the "gold standard" method considered for confirmation of MM diagnosis, which allows identification of monoclonal protein and the heavy and light chains involved, with a sensitivity of 41% when used as an isolation testing and a specificity of 100%[6,7].

In the United States, about 22,000 Americans are diagnosed each year with MM, and approximately 11,000 die from this disease. Brazil does not have exact statistics, only an estimate that there are about 30,000 patients with MM under treatment[8].

Concerning the therapeutic field of MM, it has undergone significant changes over the last ten years, directly influencing the increased survival and improving the quality of life for patients. Life expectancy increased from less than three years for up to seven years on average. This fact was possible after the introduction of new medication such as thalidomide, lenalidomide, bortezomib and autologous bone marrow transplantation as a therapeutic option[8].

The MM is a heterogeneous disease, and patients are not treated in the same way[9]. Therefore, the International Myeloma Working Group (IMWG) prepared the International Staging System (ISS), which is a more objective classification of patients based on ß2-microglobulin and albumin levels, classifying patients with MM in three groups with different overall survival: 62 months, 44 months and 29 months for the stages 1, 2 and 3, respectively. Currently, it is the staging system most used for patients with MM[10].

The MM has no cure. Thus, the main challenge for the health team is to keep patients in treatment and provide them a survival with quality. For this, it is necessary to know and characterize the population affected by this condition. Thus, this study aimed to characterize patients clinically with Multiple Myeloma treated at a referral center in the state of Rio Grande do Norte, and to estimate their survival.

METHODS

It is a retrospective cohort study of the evidence base that included patients with a diagnosis of Multiple Myeloma (MM), assisted by the hematology department of a referral service in the state of Rio Grande do Norte, Brazil, from January 2001 to December 2014.

To collect data from the participants in the study, secondary sources of the registration database in specialized medical service to care for patients with MM were used and complementation with data records.

Patients from both genders and all ages accompanied or followed up within the period studied, with a confirmed medical diagnosis of the disease in question, and available in full were included in the sample. Those who did not have a confirmed diagnosis, as well as a suggestive or diagnostic elucidation and those who did not have all the information needed to reach the proposed goals were excluded. The final sample consisted of 39 patients. The data collection period occurred between January and March 2015.

The diagnostic confirmation dates, the follow-up time in service and time of closure for the cases of death and abandonment were analyzed.

Data was organized through Microsoft Excel® for descriptive analysis using Epi Info 2002 program, version 3.5.2. For survival analysis, the Statistic Package for Social Sciences software (SPSS), version 22 was used. The survival calculations were determined by Kaplan-Meier method when the starting point was the date of the medical diagnosis confirmation and the final date of death or abandonment. The comparison of survival was performed using the statistical method for the Log Rank[11,12]. The significance level 0.05 was considered for this study.

The research protocol of this study was approved by the Research Ethics Committee of the North Riograndense League Against Cancer in its ethical and methodological aspects, according to the resolution in CNS 466/2012, under n° 827,933 and CAAE 36181314.6.0000.5293.

RESULTS

Out of 39 patients studied, 17 (43.6%) were male and 22 (56.4%) female. The age ranged between 37 and 82 years old, with an average of 66.3 and a higher frequency (76.6%) aged over 60 years old.

Table 1 describes the sample, describing the frequency of age groups, gender, hematopoietic stem cell transplantation, post-transplant response and drug treatment.

Table 2 addresses the cumulative probability of overall survival of the patients and gender. Significant value for the association of the gender variable in the outcome of survival was not found, as shown in Figures 1 and 2.

Table 1. Clinical and epidemiological characteristics of patients with Multiple Myeloma. Natal/RN, Brasil - 2015 (n=39).

Characteristics	Male (n=17)		Female (n=22)		Total (n=39)	
	N	%	N	%	N	%
Age group						
< 40 years old	1	2.6	-	-	1	2.6
= 40 < 60 years old	4	10.4	4	10.4	8	20.8
≥ 60 years old	12	31.2	18	46.8	30	76.6
Average ± standard deviation	67.5 ± 9.8		64.8 ± 13.0		66.3 ± 11.2	

Drug regimen	**Patients**	**%**
Cyclophosphamide, Thalidomide and Dexamethasone (CTD)	25	63.6
Melphalan and Prednisone (MP)	1	2.6
Melphalan, Prednisone and Thalidomide (MPT)	8	20.8
Thalidomide and Dexamethasone (TAL/DEX)	3	7.8
Vincristine, Adriamycin and Dexamethasone (VAD)	2	5.2
Comorbidity	**Patients**	**%**
Yes	15	38.5
No	24	61.5
Development of plasmacytoma	**Patients**	**%**
Yes	18	46.2
No	21	53.8
Staging - International Staging System (ISS)	**Patients**	**%**
Stage I	1	2.6
Stage II	9	23.1
State III	12	30.8
Not classified/evaluated	17	43.5
Hematopoietic Stem Cell Transplantation	**Patients**	**%**
Yes	8	20.4
No	31	79.6
Post-transplantation response	**Patients (n=8)**	**%**
Complete	4	50.0
Partial	3	37.5
Ineffective	1	12.5

Table 2. Cumulative probability of survival of patients with Multiple Myeloma. Natal/RN - 2015 (n=39)

Follow-up time (months/years)	Cumulative Probability of Survival			*Log Rank* p
	TOTAL (n=39)	Male (n=17)	Female (n=22)	
12 (1 year)	0.97	0.95	0.98	0.747
24 (2 years)	0.72	0.76	0.68	
48 (4 years)	0.34	0.43	0.28	
72 (6 years)	0.19	0.21	0.17	
120 (10 years)	0.09	0.10	0.08	

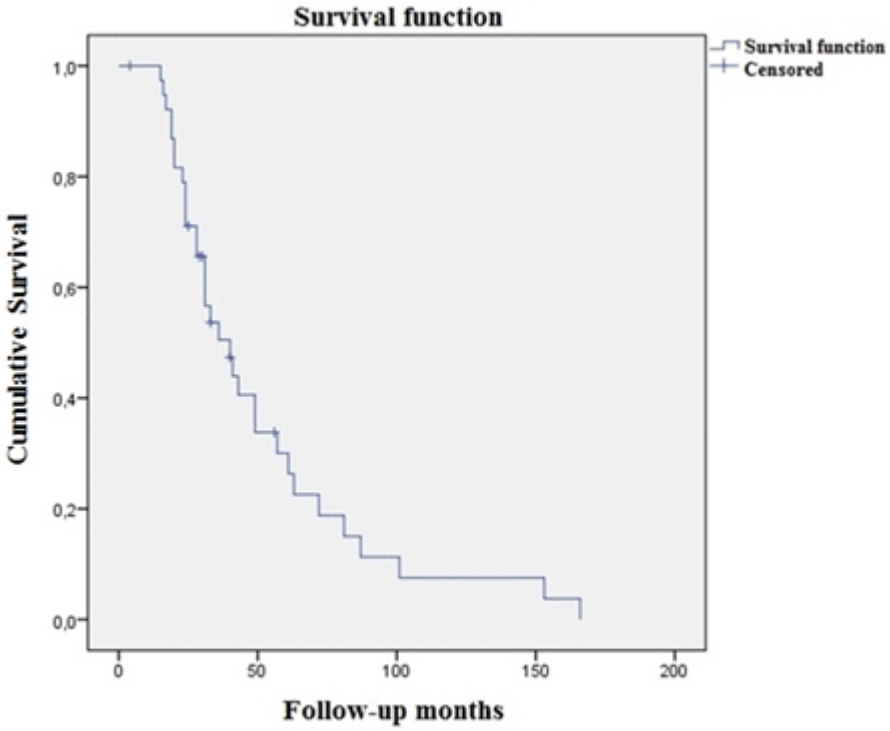

Fig. 1. Cohort survival curve analyzed between 2001 and 2014 (n= 39).

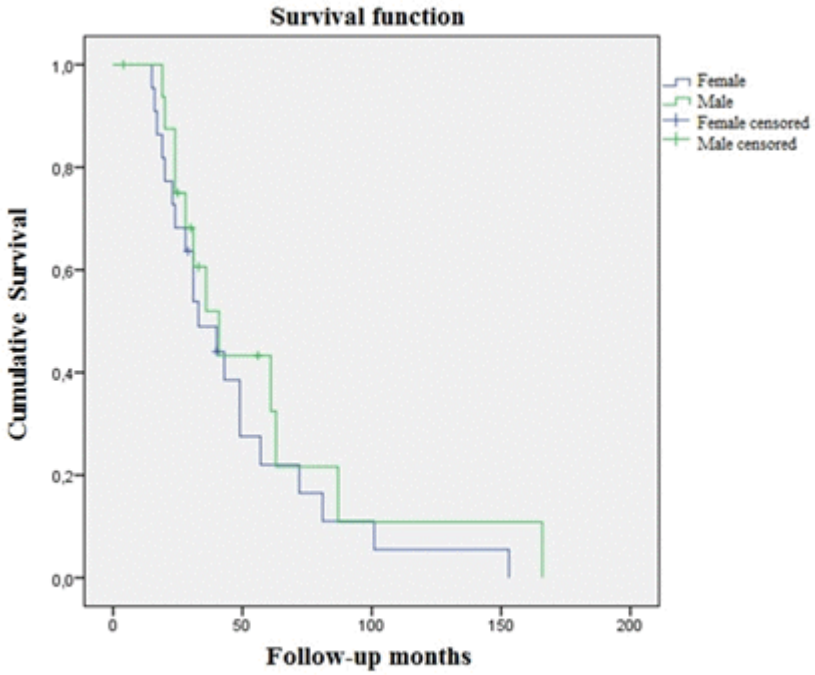

Fig. 2. Survival curve for the cohort of gender analyzed between 2001 and 2014 (n= 39).

DISCUSSION

The data presented in the study indicated that the MM often affects elderly patients when the average age of the sample was 66.3 years old, and only 2.6% were younger than 40 years old. A study in Cuba found that the mean age of patients was 60.7 years old, and only 6.8% of cases were under 40 years old (13). A study in southern Brazil showed a mean age of the study sample of 68.3 years old, emphasizing the frequency of MM in the elderly population[14].

However, a study conducted in China found an average age of 59 years old and brings as a possible explanation for this result, unlike Western countries, ethnic diversity, but more in-depth investigations are needed for the explanation of this difference[15].

Regarding gender, there was a slight predominance of females (56.4%), which diverges from the literature and may have its occurrence justified by the size of the sample. In the study conducted in China, there was a predominance of males (53.5%), while in Cuba, the ratio found was 1.7:1 for males[13,15].

On the therapeutic drug regimen, the combination of cyclophosphamide, thalidomide, and dexamethasone (CTD) was the most therapeutic indication used by patients with a percentage of 63.6% of cases, while 20.4% were submitted to Hematopoietic Stem Cells Transplantation and 50% had a complete response after transplantation.

Similar to this result, a survey conducted in Japan evaluated the effects of prognostic factors on the outcome of patients with MM after Autologous Hematopoietic Stem Cell Transplantation (HSCT), and 44.7% of patients achieved a complete response, 24.7% had very good partial response and 21.2% had partial response and concluded that high-dose chemotherapy supported by autologous stem cells in patients with advanced MM are safe, effective and are associated with a high rate of complete response [16].

Within the sample assessed, only 38.5% of patients had other comorbidities related to the MM prognosis. However, a study carried out in Italy showed vulnerability characteristics such as the number of co-morbidities, increases with age, but 30% of patients younger than 65 years old may have the same characteristics, suggesting that chronological age does not fully explain the vulnerability of the patient, but these characteristics significantly affect the survival of the patient, regardless of age [17].

It was found a frequency of 46.2% of patients who developed plasmacytoma as opposed to 53.8% who did not in this study. This finding converges with that found in another study, in which in a sample of 88 patients, only 13 cases were diagnosed with plasmacytoma, located mainly in the ribs (25%) followed by the vertebrae (18.8%), skull (12.5 %) and the same percentage (6.3%) in the sphenoid, the humerus, the clavicle, lung, central nervous system (meninges), skin and testicles[13].

The cumulative probability of overall survival found in this study showed a disease with a survival rate of 50% around 36 months (three years) after the diagnosis confirmed, no major differences compared between the genders, despite a slightly increased survival of male patients, with no statistical significance for this value ($p=0.747$). In general, the cumulative probability of overall survival was 97%, 72%, 34%, 19% and 9% for intervals of 12, 24, 48, 72 and 120 months, respectively.

A study conducted in southern Brazil on the survival of MM patients showed a median survival of 37.53 ± 29.41 months with a range from one to 122 months from diagnosis. The main study variable that showed statistical significance for survival was the presence of renal failure as a comorbidity (p=0.026), in which the average survival of patients who developed it was 39.26 months[14], approximate results found in this study.

Against these results, another study with a larger sample (88 patients) showed that patients younger than 70 years old had a higher survival rate (6.5 years) compared to the cases that were younger, with a survival of 3.8 years, although they were not as significant from a statistical point of view (p=0.188)[13].

The main limitations of this study are linked to the number of subjects in the final sample (n=39) analyzed, which in the case of a low value compromises the interpretation of data so that they can be generalized inferences and generate more property. The main biases are also associated with the fact that this is a retrospective study with secondary data collection, despite the care for the insertion of the subjects analyzed are only those provided complete, clear and explanatory data to reach the proposed goals.

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