Multiple myeloma: five-year experience at a University Hospital

Mieloma múltiplo: experiência de cinco anos em um Hospital Universitário

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ABSTRACT

Objective: To present a descriptive analysis of patients diagnosed with multiple myeloma, correlating it with mortality. **Methods:** A retrospective study that analyzed consecutive patients diagnosed with multiple myeloma under follow-up at the Faculdade de Medicina do ABC from 2006 to 2010. **Results:** The median age was 58.5 years. Anemia was observed upon diagnosis in 87% of patients, hypercalcemia in 38%, and creatinine levels higher than 2 mg/dL in 19%. M protein was detected in 85.7%. The five-year survival rate was 74.6%. Multivariate analysis showed statistical significance for Durie-Salmon staging (p = 0.037). The International Staging System and immunoglobulin type did not correlate significantly with survival of the group. **Conclusion:** This set of cases from a tertiary public healthcare service reflect the approach of multiple myeloma in a predominantly young population with advanced clinical staging, with results comparable to those of the literature.

Keywords: Multiple myeloma/therapy; Neoplasm staging; Survival

RESUMO

Objetivo: Apresentar uma análise descritiva de pacientes com diagnóstico de mieloma múltiplo, correlacionando à mortalidade. **Métodos:** Estudo retrospectivo que analisou pacientes consecutivos com diagnóstico de mieloma múltiplo, em seguimento na Faculdade de Medicina do ABC, entre os anos de 2006 a 2010. **Resultados:** A mediana de idade foi de 58,5 anos. A anemia foi observada ao diagnóstico de 87% dos pacientes, hipercalcemia em 38% e níveis de creatinina superior a 2 mg/dL em 19%. A proteína M foi detectada em 85,7%. A taxa de sobrevida em 5 anos foi de 74,6%. A análise multivariada demonstrou significância estatística para o estadiamento de Durie-Salmon (p = 0,037). O *International Staging System* e o tipo de imunoglobulina não se correlacionaram significativamente com a sobrevida do grupo. **Conclusão:** Esta casuística de um serviço público terciário reflete a abordagem do mieloma múltiplo em uma população predominantemente jovem e com estadiamento clínico avançado, com resultados comparáveis aos da literatura.

Descritores: Mieloma múltiplo/terapia; Estadiamento de neoplasias; Sobrevida

INTRODUCTION

Multiple myeloma (MM) is defined as a malignant and incurable disease of B cells, characterized by proliferation of plasma cells that secrete monoclonal immunoglobulin into the blood or urine[1], which can occur as the evolution of a monoclonal gammopathy of undetermined significance (MGUS)[2].

Myeloma corresponds to 10% of hematologic neoplasms, and its incidence increases with age, with a median age of 67 years; however, 3% of the patients at diagnosis are under the age of 40 years[3,4]. The progression rate of MGUS for MM is estimated at 0.6 to 3% a year[4,5].

Knowledge of pathophysiology of the myeloma and its secondary clinical manifestations enabled the creation of the Durie-Salmon staging system (DSS) in 1975[4]. The DSS subdivides patients into three groups, according to the values of hemoglobin, serum calcium, creatinine, levels of paraprotein, and extension of lytic bone lesions, and for more than 25 years it was the primary form of

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classification. In 2005, however, the International Staging System (ISS) was published, which also proposes three stages, but is based on laboratorial markers of disease activity: beta-2 microglobulin and albumin[4].

The ISS is validated for various population groups, including the Brazilian population, and is considered the most modern and trustworthy form of staging when compared to DSS[6]. Currently, risk stratification is added to cytogenetic evaluation with the objective of detecting survival-modifying genetic markers, such as hypodiploidia, deletion of chromosome 13 or 17p13, and translocations (4,14), (4,16)[7].

The advent of therapy with the so-called "new drugs" (thalidomide, lenalidomide, and bortezomib) and the high rates of response produced by regimes that incorporate them have revolutionized the treatment of myeloma, and have led to a reevaluation, in some cases, of the indication of autologous bone marrow transplantation (ABMT).

Currently, literature shows that the primary objective in the initial treatment of myeloma is to reach a complete response, regardless of the initial therapeutic regime chosen[4].

OBJECTIVE

To present a descriptive analysis of patients diagnosed with MM followed at a hematology outpatient clinic with priority of data related to diagnosis, staging, and treatment, as well as a correlation with survival.

METHODS

An observational cohort study based on the analysis of records of data from 77 clinical files of patients with MM followed at the Ambulatório Universitário de Hematologia da Faculdade de Medicina do ABC (FMABC) from January 2006 to October 2010.

The medical files were retrieved at the Medical and Statistical Archives Service (SAME) of the Faculdade de Medicina do ABC and, in case of posterior hospitalization and death, from the SAME of the Hospital Estadual Mario Covas, a reference hospital.

Exclusion factors used were incomplete data, noncompliance with outpatient visits, and diagnosis of non-MM plasmatic cell dyscrasias (MGUS, solitary plasmocytoma, and plasma cell leukemia), as well as cases of smoldering mieloma.

Of the total number of patients, 14 were excluded as per the following criteria: 2 for MGUS, 3 for isolated plasmocytoma, 1 for plasma cell leukemia, 2 for smoldering myeloma, and 6 for incomplete data or no follow-up, resulting in 63 patients analyzed.

At the time of diagnosis, patients were assessed as to age, gender, associated comorbidities, clinical manifestations, and laboratory parameters (hemogram/CBC, creatinine, 24-hour proteinuria, total or ionizable calcium, serum or urine electrophoresis or immunoelectrophoresis, immunoglobulin dosing, albumin, beta-2 microglobulin or plasmocytes in bone marrow). Due to differences among laboratory methods for analyzing calcium, we chose to merely describe the presence or absence of hypercalcemia. The laboratory results obtained after the diagnosis were recorded as absent since they did not reflect the true condition of patients at diagnosis.

For staging, criteria established by DSS and by ISS were used. Bone lesions seen by imaging methods (long bone X-rays) were separated as per criteria also proposed by Durie-Salmon: (0) normal bone, (I) osteopenia, (II) osteolytic lesions, and (III) skeletal destruction[8].

As to treatment, evaluation was made of the chemotherapy schemes employed, number of chemotherapy lines, referrals for transplants, and response obtained with induction chemotherapy and transplantation.

Refractory myelomas were considered those non-responsive to two lines of chemotherapy, in which the second line was rescue therapy, or those who relapsed within less than 60 days. The response to chemotherapy was classified according to the criteria established by the International Myeloma Working Group[4]. However, due to unavailability of the immunofixation technique at the institution evaluated, there was a deficiency in the criteria applied for a complete answer.

Patient evolution was documented according to the date of the last follow-up visit, which included the data of the last outpatient visit or the time of death. In cases where the patient was lost to follow-up, the date considered was the last time in which the patient was evaluated at the institution. Data on deaths were retrieved by a search in the reference hospital hospitalization service (Hospital Estadual Mario Covas) or by reports from family members.

Statistical analysis was conducted by means of data coding and application of the Statistical Package for the Social Sciences (SPSS) program. Clinical, laboratorial, and therapeutic characteristics were analyzed descriptively. The independent variables (age, comorbidity, staging, treatment utilized, and lines of chemotherapy) were assessed with bivariate analysis using Pearson's $\chi 2$ test. Survival was observed by Kaplan-Meir's method. The level of confidence adopted was 95%.

RESULTS

Population characteristics

Diagnostic criteria for MM were satisfied in 63 cases followed at the Ambulatório Universitário de Hematologia da FMABC during the period of January 2006 to October 2010.

In this population, age varied from 34 to 85 yeas (median: 58.5 years), distributed as 44% (n = 28) of the female gender and 56% (n = 35) of the male gender (Table 1).

Table 1. Demographic and laboratory characteristics of patients diagnosed with multiple myeloma followed-up at the University Hematology Outpatients' Clinic - Faculdade de Medicina do ABC

Characteristics	n	%
Age (years)	63	
< 40		5
40 – 49		14
50 - 59		29
60 - 69		25
70 - 79		24
> ou = 80		3
Sex	73	
Male		56
Female		44
Laboratory parameters	n	%
Hemoglobin (g/dL)	55	
< 8.5 g/dL		25
> 10 g/dL		31
Platelets (× 109/L)	54	
< 100		5
> 100		95
Leukocytes (× 109/L)	54	
< 4		17
> 10		9
Creatinine (g/dL)	53	
< 2		81
> 2		19
Hypercalcemia	58	
Present		32
Absent		68
Immunoglobulin (subtype)	54	
IgG		48.1
IGA		24.1
Light chain		22.2
Non secreting		5.6
Bone lesions	61	
0		6
I		20
II		13
III		61
Staging		
DSS	61	
I		1.6
II		19.7
III		78.7
ISS	45	
I		28.9
II		22.2
III		10

DSS - Durie-Salmon stage
ISS - International Staging System

In 62% of the patients, associated comorbidities were present. The most prevalent were systemic arterial hypertension (n = 22), diabetes mellitus (n = 12), and hypothyroidism (n = 7); eight patients had an association between diabetes mellitus and systemic arterial hypertension and five between hypothyroidism and systemic arterial hypertension and/or diabetes mellitus. Among the other comorbidities, we point out HIV (n = 2), cardiovascular disease (n = 3), and thromboembolic events (n = 3). The antecedent of non-hematological neoplasm occurred in five cases; two of these were of the breast, two of the prostate, and one of the skin.

Anemia was observed in 87% of the cases. At diagnosis, mean hemoglobin values were 9.6 g/dL (4.2 to 14.6 g/dL) (Table 1), and were similar for female and male genders.

The mean value of creatinine levels was 1.6 g/dL (0.6 to 8.9 g/dL); of these, 19% had creatinine ≥ 2 mg/dL (Table 1). Levels higher than 150 mg/day of protein in 24-hour urine specimens occurred in 80% of the 30 patients evaluable. On the other hand, hypercalcemia was evidenced in 38% of the 52 patients analyzed.

Albumin levels under 3.5 g/dL were noted in 41.8% of the valid population, with a mean value of 3/4 g/dL (1.3 to 4.7 g/dL). Beta-2 levels inferior to 3,500 mg/dL occurred in 30.4% and superior to 5,500 mg/dL were seen in 19.7%, with a mean of 5,419.6 mg/dL (1,851 to 20,000 mg/dL) (Table 1).

The presence of immunoglobulin peaks in serum protein electrophoresis occurred in 88% of the 51 cases evaluable; of these, 84.4% were in gamma, 9.8% in beta, and in 5.8% there was no separation. In urine protein electrophoresis, there was a peak in 29% of the 18 cases evaluable, with a predominance of the gamma fraction (75%).

The subdivision as to the type of immunoglobulin secreted was retrievable in 85.7% (n = 54) of the patients. Of these, 25.9% (n = 14) were non-defined IgG, 11.1% (n = 6) IgG kappa, 11.1% (n = 6) IgG lambda, 11.1% (n = 6) IgA without definition, 7.4% (n = 4) IgA kappa, 5.6% (n = 2) IgA lambda, and 22.2% only secreted light chains (Table 1). None of the patients evaluated secreted IgE or IgD.

Patients classified as non-secretors were 5.6% (n = 3); in these, there was evidence of anemia in one case, and there was no modification of renal function in any of these patients (Table 1).

The presence of more than 10% of plasmocytes in bone marrow was seen in 81.8% of the 44 evaluable patients, with a mean of 39.3% (0 a 92%). There was evidence of associated plasmocytoma in 31.7% (n = 20) of the total, and in two cases this fact preceded the diagnosis of myeloma.

The radiological study of the skeleton demonstrated 74% of osteolytic lesions (45/61), with predominance of advanced bone lesions (Table 1).

Staging of patients as per the criteria of Durie-Salmon and ISS is presented on Table 1. We point out that 78.7% of the patients had DSS III (n = 48), with

62.3% of them in stage A (n = 38) and 16.4% in stage B (n =10); whereas according to ISS, the 45 evaluable patients were divided into stage I (28.9%; n = 13), stage II (48.9%, n = 22), and stage III (22.2%; n = 10).

Treatment

The treatment used in patients with diagnoses of myeloma is presented on table 2.

Table 2. Chemotherapeutical regimens used as first and second line treatment of multiple myeloma patients followed up at the University Hematology Outpatients' Clinic - Faculdade de Medicina do ABC

Chemotherapeutical regimens	n	%
First line		
VAD	9	14.5
Dexamethasone	10	16.1
Thalidomide and dexamethasone	22	35.5
Melphalan and prednisone	18	29.0
Others	3	4.8
Total	62	100
Second line		
VAD	3	8.9
Cyclophosphamide and dexamethasone	3	8.9
Dexamethasone	4	11.7
Melphalan and prednisone	5	14.7
Thalidomide and dexamethasone	9	26.4
Thalidomide	10	29.4
Total	34	100

VAD - vincristine, adriamycin and dexamethasone

As first line of therapy, the main treatments used were the association of thalidomide with dexamethasone (35.5%) and of melphalan and prednisone (29%). After induction treatment, 12 of the 62 patients treated (19.3%) were consolidated with ABMT.

The patients that used thalidomide and dexamethasone had a median age of 57 years (36 to 56 years) with a predominance of stage III as per Durie-Salmon (90.9%; n = 22). At the time of assessment, 36.3% (n = 8) were using the medication. Of the 14 patients that had completed treatment, 50% had obtained some form of response (partial and complete), 35.7% had clinical stability, and 14.3% had progressed.

The median age of the population under first-line treatment with melphalan and prednisone was 69.5 years (41 to 85 years), also with a predominance of stage III (61%; n = 18). In this group of patients, the response rate was 38.9%; however, no patient satisfied the criteria for disease progression.

Overall, in evaluating the total population of patients evaluable for response, in 50 cases, a 42% response rate was attained among the various regimes.

A second line of induction was used in 34 patients, in which 55.8% used thalidomide alone or associated, and 23.5% used alchilating agents (melphalan and cyclophosphamide) (Table 2).

The total response rate to a second line was 53.1%. Among these patients, it was noted that half had received dexamethasone alone as first-line treatment.

Two more treatments were necessary in 22 patients, in which 74.6% belonged to stage III and 82.3% satisfied criteria for refractoriness.

The use of bisphosphonate occurred in 62.3% of the population studied, and radiotherapy, in 15.8%.

Survival

With a clinical follow-up that varied from 1 to 145 months, the overall survival rate was 73%, and the survival median was not reached. In 60 months, the rate of survival was 74.6% (Figure 1).

There was no difference with statistical significance between the rate of mortality and the presence of

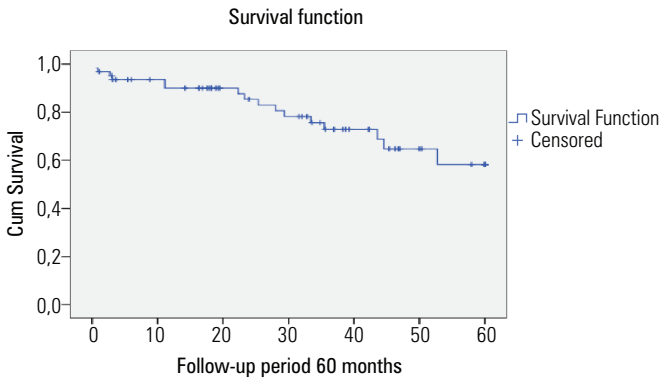

Figure 1. Survival curve in 60 months of patients diagnosed with multiple myeloma followed up at the University Hematology Outpatients' Clinic - *Faculdade de Medicina do ABC*.

comorbidities (p = 0.222), ISS (p = 0.898), and the type of immunoglobulin (p = 0.348).

In the population studied, there was a predominance of advanced stages of the disease according to Durie-Salmon criteria (78.7% stage III). In these, there were 100% of deaths, divided into 93.3% of stage IIIA and 6.7% of stage IIIB, with statistical significance (p = 0.037). As to the other stages, 1.6% belonged to the stage I and 19.7%, to stage II (Figure 2).

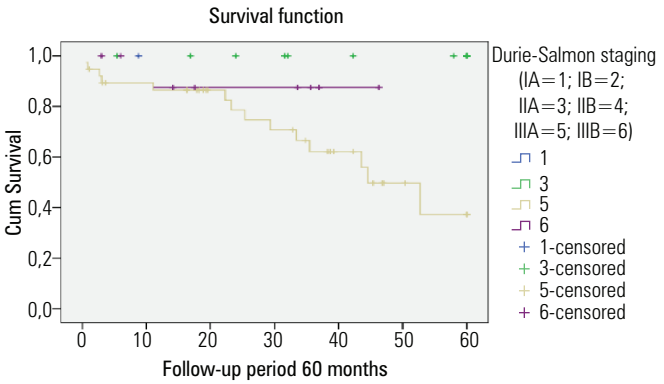

Figure 2. Survival curve in 60 months per Durie-Salmon staging.

At the end of follow-up of the cases consolidated with transplantation, 72.3% were alive. This fact did not demonstrate statistical significance (p = 0.364), as well as the response obtained prior to the transplant (p = 0.083).

The use of bisphosphonates also did not interfere with survival (p = 0,567).

DISCUSSION

The median age found in follow-up of the 63 patients diagnosed with MM showed data slightly inferior to that reported in national literature, in which a study carried out by Hungria et al. with 16 Brazilian institutions demonstrated a median of 60.5 years[9]. On the other hand, the publication by Kyle et al., at the Mayo Clinic, reported a median age of 66 years (20 to 92 years), with a case distribution of 38% over 70 years of age, surpassing the findings in this study by 11%[10].

As expected, according to the age bracket of myeloma incidence, most patients presented with associated comorbidities, such as hypertension and diabetes. Nevertheless, it was noted that 3.2% were seropositive for HIV.

Among the diagnostic data evaluated, most of the patients presented with anemia, which is known to be the most common hematological complication in MM[4]. Although the current findings have proved greater than those in literature, when compared to the data of Brazilian groups, it was noted that the percentage found was greater than the data found at the Federal University of Minas Gerais (UFMG), where 81.2% had hemoglobin levels lower than 12 mg/dL, although lower than those of the University of the South of Santa Catarina state (Unisul) – 95.7%[11,12].

There are various mechanisms that explain the drop in values of hemoglobin in myelomas, such as inadequate use of iron, deficiency of erythropoietin, hemolysis, and bone marrow infiltration, in which the latter may be associated or not with the other cytopenias[4]. In this study, 5% coursed with plateletopenia and 17% with leukopenia; these finding are concurrent with other similar publications[10,13].

As was true with anemia, renal disease is secondary to lesion of the target-organ in myeloma, as was demonstrated in this study by the mean values of creatinine and with 19% of the cases with levels higher than 2 mg/dL[4].

Despite a mean value of creatinine greater than that found by the Mayo Clinic (1.2 mg/dL), the percentage greater than 2 mg/dL was similar[10]. Nevertheless, this datum is not in agreement with the description given by Hungria et al. for the Brazilian population, according to which creatinine values higher than 2 g/dL occur with greater frequency (23%)[13].

Additionally, Hungria et al. reported the presence of hypercalcemia in 23.8% of the patients assessed in his multicentric study, a figure that is inferior to those identified in our group and to those of Kyle et al. (28%)[10,13].

Complementing the clinical evaluation, almost all patients presented with bone lesions, 74% with lytic lesions, and 61% of Grade III. Such findings are greater than and not similar to those of Kyle et al. (66% of lytic lesions) nor those of Hungria et al., in which the bone lesion values described are greater than those found in international medical literature (85.1%)[10,13].

The M protein was detected in a large number of cases, demonstrating agreement with literature as to the predominance of MM producers of IgG (48.1%), but there was disagreement with Kyle et al. as to the producers of isolated light chains, described as 16%, a datum inferior to that of this study[10].

As to staging, there was predominance of stage III by Durie-Salmon and II by the ISS criteria.

Our findings are relatively similar to the multicentric Brazilian study in which stage III of the Durie-Salmon system occurred in 76.5%, and ISS was distributed as follows: 20.1% in stage I, 48.7% in stage II, and 31.2% in stage III [13].

Medical literature defends the position that ISS is a more trustworthy prognostic method, since, besides reflecting the related survival, this staging system does not use data that cause biases in the related survival, such as hypercalcemia, which is considered an independent factor of poor prognosis[13-14]. The ISS system, however, is validated for the Brazilian population[13].

Analyzing the overall survival found in this study, we identified a rate of practically 75% in 60 months. These data compare favorably with those of literature, since, according to epidemiological data published by Brenner et al., relative survival in 5 years after the advent of the new drugs is 48.2%, and in 10 years, 28.6%[15].

Among the reasons that can explain the correlations described, we find the smallest number of cases in which the ISS classification is known, since clinical staging can be retrieved 61 patients and the ISS in only 45, which reduces the statistical power to detect significant survival differences between more or less severe stages of the disease.

Despite the data described having traced the prognosis in MM, currently, literature has emphasized the importance of treatment in the evolution of symptomatic patients. This is because prior to the use of alchilating agents, survival was lower than 1 year, and it attained an accentuated increase with the advances that have occurred, especially transplantation and the "new drugs"[15].

Kumar et al. compared two groups of MM patients as to the moment when they relapsed, defined as before the year 2000 or after the year 2000, meaning, before or

after the new drugs, noting that the second group had a mean survival of 23.9 months versus 11.8 months in the first group[16].

In this paper, with the exception of one case that used bortezomib at the time of diagnosis, due to availability in the public healthcare services, the drug used, from the most modern group, was thalidomide, with the alchilating agents reserved for the group of patients not eligible for ABMT. Therefore, the median age of patients with thalidomide was 57 years, and with melphalan, it was 69.5 years.

Accordingly, the response rate to the schemes of melphalan/prednisone and thalidomide/dexamethasone is in agreement with literature references, albeit at the lower limit. The first obtained with first-line treatment a rate of 38.9%, similar to that in literature that reports response rates that varied from 35 to 47%, and the second obtained a 50% response rate, similar to series in literature that report rates of 48.5 to 72%[4,17].

CONCLUSION

The analysis of patients with a diagnosis of MM followed in the outpatient clinic of hematology identified staging of the cases, treatment, and rates of survival similar to those in medical literature, with the resources available at a public and university healthcare institution.

REFERENCES

1. Damiano JS, Cress AE, Hazlehurst LA, Shtil AA, Dalton WS. Cell adhesion mediated drug resistance (CAM-DR): role of integrins and resistance to apoptosis in human myeloma cell lines. Blood. 1999;93(5):1658-67.
2. Hideshima T, Mitsiades C, Tonon G, Richardson PG, Anderson KC. Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. Nat Rev Cancer. 2007;7(8):585-98.
3. Palumbo A, Rajkumar SV. Treatment of newly diagnosed myeloma. Leukemia. 2009;23(3):449-56.
4. Caers J, Vande broek I, De Raeve H, Michaux L, Trullemans F, Schots R, et al. Multiple myeloma--an update on diagnosis and treatment. Eur J Haematol. 2008;81(5):329-43.
5. Dispenzieri A, Katzmann JA, Kyle RA, Larson DR, Melton LJ 3rd, Colby CL, et al. Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. Lancet. 2010;375(9727):1721-8.
6. Hari PN, Zhang MJ, Roy V, Pérez WS, Bashey A, To LB, et al. Is the International Staging System superior to the Durie-Salmon staging system? A comparison in multiple myeloma patients undergoing autologous transplant. Leukemia. 2009;23(8):1528-34.
7. Stewart AK, Bergsagel PL, Greipp PR, Dispenzieri A, Gertz MA, Hayman SR, et al. A practical guide to defining high-risk myeloma for clinical trials, patient counseling and choice of therapy. Leukemia. 2007;21(3):529-34.
8. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer. 1975;36(3):842-54.
9. Hungria VT, Maiolino A, Martinez G, Colleoni GW, Coelho EO, Rocha L, Nunes R, Bittencourt R, Oliveira LC, Faria RM, Pasquini R, Magalhães SM, Souza CA, Pinto Neto JV, Barreto L, Andrade E, Portella Mdo S, Bolejack V, Durie BG; International Myeloma Working Group Latin America. Mieloma múltiplo: progressos e desafios. Rev Bras Hematol Hemoter. 2007;29(1):1-2.
10. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(1):21-33.
11. Silva RO, Brandão KM, Pinto PV, Faria RM, Clementino NC, Silva CM, et al. Mieloma múltiplo: características clínicas e laboratoriais ao diagnóstico e estudo prognóstico. Rev Bras Hematol Hemoter. 2009;31(2):63-8.
12. Sakae TM, Santos NA, Baldessar MZ. Sobrevida de pacientes portadores de mieloma múltiplo atendidos em hospital de referência no sul de Santa Catarina. Rev Bras Clin Med. 2010;8(3):216-21.
13. Hungria VT, Maiolino A, Martinez G, Colleoni GW, Coelho EO, Rocha L, Nunes R, Bittencourt R, Oliveira LC, Faria RM, Pasquini R, Magalhães SM, Souza CA, Pinto Neto JV, Barreto L, Andrade E, Portella Mdo S, Bolejack V, Durie BG; International Myeloma Working Group Latin America. Confirmation of the utility of the International Staging System and identification of a unique pattern of disease in Brazilian patients with multiple myeloma. Haematologica. 2008 ;93(5):791-2.
14. Rajkumar SV. Multiple myeloma. Curr Probl Cancer. 2009;33(1):7-64.
15. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood. 2008;111(5):2521-6.
16. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516-20.
17. Weber D, Rankin K, Gavino M, Delasalle K, Alexanian R. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol. 2003;21(1):16-9.