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Research Article

Clinical and Laboratory Analysis of Patients with Multiplemyeloma: Five-Year Experience

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Abstract

Background: Multiple myeloma (MM) is characterized by clonal expansion of plasma cell in the bone marrow and production of monoclonal immunoglobulin, with bone destruction, renal failure and suppression of the normal hematopoiesis. Identification of clinical factors and laboratory diagnosis is important to characterize the stage of the disease and estimate survival.

Objective: To identify clinical and laboratory diagnosis of patients with multiple myeloma treated at HEMOPE - Foundation of Hematology and Hematology of Pernambuco.

Methods: This was an observational, transversal study with secondary data obtained from medical records. A descriptive analysis of clinical and laboratory features and prognostic factors of 112 patients diagnosed with multiple myeloma was conducted from January 2010 to December 2014.

Results: The median age was 65 years, of these 49.1% were male and 50.9% female. The most common clinical manifestations were: bone pain (70.5%), weight loss (25%) and weakness (23.2%). Anemia has been observed at diagnosis in 75% of patients and hypercalcemia in 15.2%. Regarding the staging system at diagnosis, 94 (83.9%) patients were classified as stage III Durie-Salmon and 32 (28.6%) patients in stage II of the International Staging System (ISS).

Conclusion: Our found in this study were similar to previous reported in the literature. A good characterization of the patient's diagnosis and the use of accurate diagnostic methods are the ideal approach for better risk classification, therapeutic choice and follow-up of patients with MM.

Introduction

Multiple Myeloma (MM) is a progressive and incurable neoplasm characterized by the dysregulated and clonal proliferation of plasma cells in the bone marrow, which produces and secrets monoclonal immunoglobulin (Ig) or M protein [1]. It is usually preceded by an asymptomatic precursor stage called (Monoclonal Gammopathy of Unknown Significance (MGUS). This initial phase may result in plasma cytoplasmic proliferation and the production of monoclonal protein in the blood and/or urine, promoting dysfunction in target organs. The MGUS progression rate for multiple myeloma is about 0.5-1% per year [2].The MM symptomatic phase includes anaemia, renal failure, recurrent infections and plasma hypercalcemia resulting from bone destruction which causes pain to the patient [1].

The identification of clinical and laboratorial factors is important to predict survival. The Durie-Salmon staging system (1975) is most commonly used and analyses the combination of factors (haemoglobin, serum calcium, monoclonal component, bone involvement and serum creatinine) that correlate to tumour mass [3]. Another classification system is The International Staging System (ISS), a new model which allows stratification of subgroups with different evolutions using only two microglobulins and serum albumin dosages [4].

Multiple Myeloma (MM) accounts for 1% of all malignancies and is slightly more than 10% of hematologic malignancies in the United States, losing only to Non-Hodgkin's Lymphomas [5]. The annual incidence in the U.S. is approximately 4 to 5 per 100,000 inhabitants. A similar incidence has been reported in Europe [6]. In Brazil, however, there is a deficiency of works about incidence of MM [7], mainly in the northeastern region. This may contribute to the large number of patients diagnosed with advanced stages of MM. The importance of this work is to help the primary and secondary care services on the identification and guidance of MM patients, as well as know when it is the best time to refer to a haematologist.

The increasing incidence of MM in recent years is related to several factors, including greater knowledge of the natural history of the disease and its pathogenesis, improvement of laboratory resources, and increased life expectancy [8]. Due to this higher incidence, it is essential to know the clinical and laboratory presentation of multiple myeloma without haematology specialized hospitals to identify the stage of the disease, and to promote the stimulation of suspicion in earlier stages for a better therapeutic approach.

Objective

The following study aims to analyse the clinical and laboratory profile of patients with Multiple Myeloma admitted to the HEMOPE (Pernambuco Haematology and Hemotherapy Foundation). Se as associações significantes do do ponto devistae statístic otive remimpacto so brees tetra balhoseriao portunoque també maquifos semmencionadascomo objetivos.

Methods

This is a cross-sectional study which aims to collect data from the analysis of patients' medical records that were diagnosed with Multiple Myeloma between January 2010 and December 2014. It was performed at HEMOPE, a referential centre in the city of Recife, northeast of Brazil.

Data collection

The VIDA® (software used to maintain electronic patient records at HEMOPE) was used to search the medical records. The search was performed according to the International Classification of Diseases (ICD 10) for Multiple Myeloma (C 90.0) and the period of admission to the service. It resulted in 145 records from which 28 (19.3%) were excluded due to the absence of diagnostic exams in the medical records and/or because they were patients with relapsed MM or diagnosed before 2010. Five medical records (3.4%) were not found in the file, resulting in a total of 112 patients.

Sample selection

The inclusion criteria used in the selection of the patient sample for the study were patients registered and diagnosed with multiple myeloma in the VIDA® software and admitted at HEMOPE in the same collect time. Patients who started chemotherapy at other hospitals were excluded from this work because the clinical information profile was not obtained.

Study variables

The analysed variables are described in Table 1 and Table 2.

Bioethical aspects

This research respects the principles of bioethics with the approving of HEMOPE ethical committee.

Statistical analysis

Data were organized using the SPSS (Statistical Package for the Social Sciences - SPSS Inc., Chicago, IL, USA) statistical software package, presented by descriptive (absolute and percentage distributions) and analytical statistics, with a margin of error of 5%. The chi-square and Fisher's exact tests were used to assess the significance of the associations.

Results

In a total of 112 patients, with a median age of 65 years (range 40-90), 49.1% (n = 55) were males and 50.9% (n = 57) were females. There was a predominance of brown colour 75.9% (n=85) and no patient identified himself as black. Regarding the place where patients came from and medical referral place, most were from Região Metropolitana do Recife 64.3% (n = 72) (Table 3) and 46.4% were referred from tertiary care (n = 52). It was not possible to identify the medical referral origin in 39.3% (n = 44) of the cases. The time from onset of symptoms to the first consultation with a haematologist ranged from <1 month to 48 months, with an average of 7.6 months. It was not possible to obtain this information in 45 charts.

Among the clinical manifestations evaluated, the most prevalent were bone pain 70.5% (n = 79), weight loss 25% (n =28), weakness 23.2% (n = 26), pathological fracture 22.3% (n = 25), and infection/fever 16.1% (n = 18). Anaemia was observed in 75% of the cases, with 57.1% (n = 64) of the patients with haemoglobin (Hb) levels lower than 8.5 g/dL at diagnosis. In one patient, there was the report of anaemia, without examination of the diagnosis. Thrombocytopenia (platelets ≤100,000 / mm^3) found in 17 (15.2%) patients (Table 3). 22 (19.6%) of patients presented creatinine ≥ 2 mg/dL, with 10 (8.9%) of these cases already manifesting chronic renal failure (CRI) at diagnosis. Many patients had creatinine <2 mg/dL (N=88; 78.6%) and

Table 1: Independent variables.

Variable Name	Definition	Categorization
Haemoglobin	Haemoglobin concentration in peripheral blood	1. Above 10 g/dL 2. Between 8.5 and 10 g/dL 3. Less than or equal to 8.5 g /dL
Serum Calcium	Concentration of calcium in peripheral blood	1. Less than or equal to 12 mg/dL 2. More than 12 mg/dL
Lytic lesions	Damaged bone areas	1. Absent 2. Present
Creatinine	Concentration of creatinine in peripheral blood	1. More than or equal to 2 mg/dL 2. Less than 2 mg/dL
Albumin	Concentration of albumin in peripheral blood	1. More than or equal to 3.5g /dL 2. Less than 3.5g/dL
β2 microglobulin	Concentration of β2 microglobulin in peripheral blood	1. Less than 3.5mg/dL 2. Between 3.5 and 5,5 mg/dL 3. More than or equal to 5.5mg/dL
Medical referral origin	Level of care that referenced the patient to the specialist	1. Primary care 2. Secondary care 3. Tertiary care

Table 2: Sets of demographics, quantitative and dependent variable.

Variable Name	Definition	Categorization
Age Group	Age of patient at diagnosis	1. Between 40 to 65 years old 2. ≥ 65 years old 3. ≥ 70 years old
Gender	Sex of the patient	1. Male 2. Female
Skin colour	Self-declaration of skin colour by the patient	1. White 2. Brown 3. Dark
Origin	Place of residence of the patient (among the five subregions of the state of Pernambuco)	1. RegiãoMetropolitana 2. Zona da Mata 3. Agreste 4. Sertão 5. São Francisco
Durie-Salmon Staging	Clinical evaluation capable of extending the disease	1. Stage I 2. Stage II 3. Stage III 4. A 5. B
ISS Staging	Evaluation capable of predicting related survival	1. ISS I 2. ISS II 3. ISS III

Table 3: Demographic and laboratory characteristics of patients with multiple myeloma at HEMOPE.

Characteristics	N	%
Age (Years)		
40-65	54	48,2
≥ 65	58	51,8
> 70	26	23,2
Gender		
Male	55	49,1
Female	57	50,9
Skin colour		
White	14	12,5
Dark	0	0
Brown	85	75,9
Origen		
Regiãometropolitana	72	64,3
Agreste	16	14,3
Zona da Mata	11	9,8
Sertão	9	8
São Francisco	4	3,6
Laboratory parameters		
Haemoglobin (g/dL)		
< 8,5	64	57,1
8,5 - 10	20	17,9
> 10	27	24,1
Platelets (x 10^9/L)		
< 100	17	15,2
> 100	95	84,8
Creatinine (mg/dL)		
< 2	88	78,6
≥ 2	22	19,6
Hypercalcemia		
Present	17	15,2
Absent	87	77,7

Table 4: Monoclonal peak in serum proteins electrophoresis in patients with Multiple Myeloma.

Location	Presence of Monoclonal Peak	
	N	%
Peak in gamma globulin	66	58,9
Peak in beta globulin	19	17
Peak absent	18	16,1
Undetermined*	9	8
Overall	112	100

*Absence of data in medical records

2 (1.8%) had no register in the medical record. 20 of the 22 (90.9%) patients with renal function abnormality had Durie-Salmon stage III at presentation. Hypercalcemia was found in 15.2% (n = 17) of the studied sample and albumin levels below 3.5 g/dL in 58.9% of the patients. In the electrophoresis of serum proteins, 66 (58.9%) patients presented a monoclonal peak in the region of gamma globulins, while the proportion of patients who presented a beta peak and the absence of monoclonal peak was very similar (Table 4).

Regarding the frequency of monoclonal (M) protein types, none of the patients evaluated secreted IgE or IgD (Table 5).

Table 5: Patients with Multiple Myeloma Distribution according to the type of monoclonal protein (M).

Protein type M	N	%
IgG	74	66,1
IgA	17	15,2
Light chain	5	4,5
IgM	1	0,9
Non-secretor	2	1,8
Undetermined *	13	11,6
Total	112	100

*Absence of data in medical records.

Table 6: The bone evaluation and examinations of patients with Multiple Myeloma.

Bone lesion evidenced in:	N	%
Skeletal radiography	30	26,5
Computed tomography	31	27,7
Magnetic Resonance Imaging	20	17,9
Scintigraphy	1	0,9
Absence of bone lesion	14	12,5
Image test not realized	27	24,1

The presence of plasma cells higher than 10% in the bone marrow was shown in 90.8% (n = 89) of the 98 evaluable patients, with a median of 38% (0 to 100%). In 9 (9.2%) cases the myelogram detected infiltration less than 10% and in 21 (21.4%) patients the percentage of plasma cells was ≥ 60%. Nine patients did not present the result of the examination in the medical record, either because they did not register. Five exams were hemming diluted and five Bone Marrow Biopsies (BMO) were performed for the diagnostic conclusion. All the biopsies presented anomalous cells of plasmocytic lineage. In 11.6% (n = 13) of the total shown plasmocytoma.

Bone lesions were detected in 71 (63.4%) patients through the following imaging exams such as simple skeletal radiography, computed tomography, magnetic resonance imaging, and scintigraphy. There was no evidence of bone lesion in 14 (12.5%) patients and 27 (24.1%) did not perform imaging tests. In the medical records, there were no detailed description of the degree of bone involvement, lytic lesions and fractures (Table 6).

Table 7: First-line treatment received by patients with Multiple Myeloma at diagnosis.

Monotherapy	N	%
Dexamethasone	17	15,2
Thalidomide	1	0,9
Bortezomibe	2	1,8
Double Therapy		
Dexamethasone + Thalidomide	23	20,5
Pm	4	3,6
Bortezomib + Dexamethasone	5	4,5
Triple Therapy		
Ctd	3	2,7
Cybord	22	19,6
Vtd	1	0,9
VMP Ou VMD	2	1,8
Mpt	16	14,3
Vad	1	0,9
Nenhum	2	1,8
Radioterapia/Cirurgia	1	0,9
Indeterminado*	12	10,7
Total	112	100

PM = Prednisone Melphalan; CTD = Cyclophosphamide, Thalidomide, Dexamethasone; CYBORD = Cyclophosphamide, Bortezomib, Dexamethasone; VMP = Bortezomib, Melphalan, Prednisone; VMD = Bortezomib, Melphalan, Dexamethasone; MPT = Melphalan, Prednisone, Thalidomide; VAD = Vincristine, Adriamycin, Dexamethasone;

*Patients who were referred to another service not being able to know the first therapy chosen.

Patient staging according to the Durie-Salmon and ISS criteria. It is noteworthy that 83.9% (n = 94) of the patients had a clinical stage of DS III, with 73.2% of the patients with MM presenting stage A (n = 82) and 17.9% stage B (n = 20). According to the ISS, patients were divided into stage I (11.6%, n = 13), stage II (28.6%, n = 32), and stage III (25.9%, n = 29). Table 7 present the various first-line treatment regimens employed in the patients studied.

In the first line, the main treatments used were the association of dexamethasone and thalidomide (20.5%), CYBORD (19.6%), dexamethasone (15.2%) and MPT (14.3%). Only 29 (25.9%) patients were referred to autologous Bone Marrow Transplantation (BMT), 4 (3.6%) of these patients refused therapy. Patients who used dexamethasone and thalidomide had a median age of 61 years (40 to 75 years; SD = 9.6), with Durie-Salmon staging III (91.3%; n = 21) predominating. The median age of the first-line treatment population with CYBORD was 57 years (44-69 years, SD = 6.6), while the MPT group had a median age of 69 (60-86 years, SD = 6.5), in both cases there was a predominance of Durie-Salmon staging III (86.4%, n = 19 / 87.5%, n = 14).

Obteve-se associaçãosignificante (p<0,05) entre o diagnóstico de MM e as variáveis: cor da peleparda, residêncianaregiãometropolitana do Recife, idade superior a 60 anos, imagenssugestivas de lesõesósseas, anemia, tratamento com o uso de Dexa (somando-se isolados e associados), Ig Igg e EP-G.

Discussion

The median age reported by European study was 70 years old when diagnosed, while in the U.S. was 66 years [9,10]. Although the case distribution over 70 years old was 38% in the American study, the data found in this work for patients over 70 years was 23% [10]. The median age of this study is slightly higher than reported in Brazilian literature. Comparing studies conducted by Hungriaet al and Todaro et al, it has demonstrated a median of 60.5 and 58.5 years old, respectively [11,12].

Regarding gender, there was an equivalence between the two genders, which may be justified by the size of the sample or characteristics of the population itself. Several Brazilian centres showed prevalence in females (52%), in contrast to the international literature reporting a slight male predominance of 1.4:1 [13]. Furthermore, a Brazilian study by Todaroet al showed a prevalence of MM to 56% in males [12].

The incidence of MM varies with ethnicity, with an increased risk of two to three times in blacks compared to whites. This racial disparity is related to the higher prevalence of monoclonal gammopathy of undetermined significance in black individuals with greater genetic predisposition. In this study, there was a predominance of patients who declared themselves to be brown, without even having a black patient record [14,15].

The majority of patients attended were from the metropolitan area of Recife, because HEMOPE is a haematological referential centre in

capital state, which facilitates access for the population who lives in the metropolitan region. Patients from Recife's other subregions may have been non-diagnosed or may die before defining their diagnosis.

Many patients (63.4%) have presented bone pain, which is known to be the main clinical manifestation of MM related to bone destruction [16]. This symptom was reported in 68% of American patients [10]. The fact that the most frequent clinical manifestation at diagnosis is bone pain confirms that the disease is at full activity and corroborates the finding of a more advanced clinical stage of the disease observed in South American patients [17]. This fact combined with the late diagnosis contributes to a considerable number of patients with pathological fracture in the presentation of the disease.

Although extra medullary MM is an uncommon manifestation, it was found considerable number of cases (11.6%) in this work when compared to a review of 432 MM patients followed up in the Department of Haematology of the French Institute with 4.4% [18]. Nevertheless, this was slightly lower than those described in the Saudi Arabia Hospital which its study shown 18.8 % [19].

The infection/fever rate found in this diagnostic study sample 16,1% (n=18) was above with number presented at Federal University of Minas Gerais (UFMG) study which documented fever in 8 (7.9%) patients, infectious or advanced stage [20].

Weakness is a MM common symptom, with reports being present in up to two-thirds of patients at diagnosis [10] Nonetheless, it was not largely referenced in the current study probably due to a lack of record in the medical register. Anaemia occurred in 75% of the patients and contributes to fatigue, which confirms the theory that there was a failure to register the symptom. The weight loss found was similar to that reported by Kyle et al (24%) [10].

Anaemia is the most common haematological complication in multiple myeloma and occurs in more than two thirds of patients, with approximately 25% of patients presenting Hb lower than 8.5 g/dL at diagnosis [21]. The highest number of anaemic found in this study (57%), compared with literature data, it can be due to delayed diagnosis, resulting in a more advanced disease.

A total of 15% of the patients were diagnosed with thrombocytopenia, a higher frequency than present by literature which is around5% thrombocytopenic patients [10,20]. Thrombocytopenia is common in advanced cases with extensive spinal cord involvement or after radiotherapy and chemotherapy.

Renal failure occurs from 25% to 75% of patients with multiple myeloma at presentation and is associated with increased mortality [22].This discrepancy in the prevalence of renal involvement is due to several factors, including the different definitions of chronic kidney disease and different methods of renal function assessment (creatinine clearance, creatinine concentration, anthropometric formula). This work presented data frequency (around 20%) similar to American and Brazilian studies of MM patients with creatinine values above 2 mg/dL [10,17].

According to American and European registries, between 0.9-1.5% of patients who initiate dialysis express multiple myeloma [22]. Almost 50% of the patients with serum creatinine ≥2mg/dL had a dialysis requirement at diagnosis and all had advanced stage III disease. This again reflects the delay in the identification of the disease and patients with major complications related to the advanced MM, with a tendency towards early mortality. An important cause of renal impairment in MM is hypercalcemia. The value obtained in this work is within the range reported in the literature, where hypercalcemia is documented between 15% and 30% of the cases [23]. According to Todaroet al, hypercalcemia was found in 32% of the total of 58 MM patients [12]. The findings of this report are also closer to number observed in Hungriaet al study that reported the presence of hypercalcemia in 23.8% of the patients evaluated [24].

In the electrophoresis of serum proteins, the finding of the largest monoclonal peak in the region of gamma globulins followed by beta globulins agrees with data obtained from the journal article [20]. The gamma globulin peak was present in 65.9% of patients' results while the beta globulins appeared in 14.1% of them. The M protein was detected in many cases, demonstrating agreement with the literature on the predominance of IgG-producing MM (66.1%). Nevertheless, the isolated light chain producers described in the articles with 16% were lower than this work [10]. About 2% to 3% of MM have undetectable M protein in electrophoresis and serum and urinary immunofixation and are defined as non-secreting [25]. This work found absence of M protein in 1.8% of the cases.

Lytic bone lesions leading to bone pain are found in about 70% of patients with MM at the onset of disease and up to 20% may have osteopenia [26]. Conventional radiological studies are universally used in the initial evaluation of the MM patient and reveal osteolytic, sacral, osteoporotic and fracture lesions in almost 80% of patients at diagnosis. Focal lytic lesions are found in about 60%; osteoporosis, pathological fractures and compressive spine fractures, each one is present in approximately 20% of patients [11]. In this work, bone lesions were found in 63.4% of patients, similar to those reported by the literature. Hungary et al. describe values of bone lesions higher than those found in the international literature (85.1%) [24]. It was not possible to categorize the degree of bone lesion due to lack of data in the medical record.

The myelogram is of fundamental importance in the definitive diagnosis of MM and in the differential diagnosis with other monoclonal gammopathies, and it may be a diagnosis for MM in up to 96% of patients. The proportion of plasma cells in MO less than 10% can occur in approximately 4% of patients, since the spinal involvement is focal and non-diffuse. The diagnosis will then depend on the patient's clinical condition associated with the morphological alterations of the cells or the MO biopsy [10]. This work shows the presence of plasmocytes greater than 10% in the bone marrow was found in 90.8% of the patients which was higher than that reported in the literature [12]. Probably the completion of bone biopsy would be fundamental for diagnostic definition in these cases.

Among patients with more than 60% of plasma cells in the bone marrow, all patients had advanced Durie-Salmon (III) stage disease, corroborating presented by journal articles which the degree of infiltration is related to disease's stage andnumber of lesions in target organ and survival [27]. There was predominance of stage III by Durie-Salmon and II according to ISS criteria. The clinical staging of Durie-Salmon (ECDS) brings together the main clinical parameters correlated to the tumour mass in the MM and all factors evaluated have relevance in the detection and evolution of the disease. The fact that most patients are at an advanced stage of the disease at diagnosis

suggests problems related to the early detection of this neoplasm in our population.

The literature argues that ISS is a more reliable method of prognosis because it reflects the related survival since it is based on laboratory markers of disease activity. This staging does not use data that cause bias in this survival, such as hypercalcemia, which is considered an independent factor of poor prognosis [12]. The data from this study are relatively similar to those found in a Brazilian multicentre study performed by Hungary et al (2008), in which the majority of MM patients were at an advanced stage at the time of diagnosis: 68 (6.4%), stage I, 182 (17.1%) stage II, and 816 (76.5%) in stage III. There was also a predominance of ISS stage II, with the following distribution: 20.1% of stage I, 48.7% of stage II and 31.2% of stage III. Prevalence of stage III by Durie-Salmon (78.7%) and II by ISS criteria (48.9%), was also reported by Todaro et al [28].

The first therapy used was similar to Todaro et al presented in their study where dexamethasone and thalidomide (35.5%) were the first-choice induction therapy in a population with a median age of 57 years [28]. In this study, triple therapy involving a proteasome inhibitor was the second most commonly used treatment, while in the study by Todaro et al, in patients with a median age of 69.5 years, the chosen regimen was melphalan and prednisone (29%), [28] a well-tolerated regimen in vulnerable elderly patients with good response rates and survival [9].

Only 25.9% of the patients were referred to autologous Bone Marrow Transplantation (BMT), a small percentage when 48.2% of patients were considered between 40-65 years of age and the chronological age for BMT Majority of countries, is 65 years. This percentage becomes even smaller when greater flexibility is admitted in the age to refer to BMT, as it occurs in the United States, considering good functional status and minimal patient comorbidity. A study conducted by Todaro et al showed similar results with 12 of the 62 treated patients (19.3%) being consolidated with autologous BMT after induction therapy [28]. Most the patients, 83 (74.1%), had no record in the registry of autologous BMT, either because they were referred to another service, lost in follow-up, or because they had a disease that was always active, persisting in therapy or death. Some were considered ineligible due to age, in view of the toxicity related to the procedure.

The fact that the clear majority of patients are referenced by tertiary care reveals the difficulty of recognizing the disease in early stages, which leads to progression of MM and diagnosis in advanced stages, either in secondary or tertiary care, when the patient is referred to the Haematologist. This results in treatment delay, higher mortality rate, and lower overall survival.

Conclusion

The most part of the patients were older than 65 years, female, brown and from the regiãometropolitana do Recife. Their haemoglobin was less than 8.5 g/dL with platelets more than 100 x 109/L, creatinine less than 2mg/dL and absent of hypercalcemia.

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