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Original Research Article

Prognostic factors in multiple myeloma and the impact of the bone involvement

Flora Palmari Audi Oliveira[1], Vitória Melina Faquini de Souza[1], Maura Lima Pereira Bueno[1,2]*, Fernanda Marconi Roversi[1,2]

[1]Universidade São Francisco, Bragança Paulista, São Paulo, Brazil
[2]Hematology and Transfusion Medicine Center, University of Campinas/Hemocentro-Unicamp, Campinas, São Paulo, Brazil

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***Correspondence:**
Dr. Maura Lima Pereira Bueno,
E-mail: mauralimabueno@gmail.com

ABSTRACT

Background: Multiple myeloma is characterized by abnormal plasmocytes proliferation in the bone marrow, resulting in an immunoglobulin oversecretion, which can cause bone pain, anemia, kidney dysfunction, and infections. The present study evaluates prognostic factors and the bone involvement in patients who had a confirmed diagnosis of MM.
Methods: A retrospective study was conducted in hospital universitário São Francisco of Bragança Paulista. Patient demographic data, laboratory parameters and treatment received were recorded. We also analyzed the variables related to diagnosis and the development of bone lesions in MM patients.
Results: A total of 42 patients had a confirmed diagnosis of MM, out of which most (54.76%) were older than 65. Most patients (45.24%) had beta-2-microglobulin values greater than 5.5 mcg/dl, indicating an advanced stage of the disease and consequently a less favorable prognosis. The main clinical manifestation observed was anemia in 61.90% (26/42) and bone lesions 59.52% (25/42). The analysis of imaging exams showed that most patients presented bone alterations, such as osteopenia, lytic lesions and fractures. Interestingly, 11.90% patients were submitted to autologous bone marrow transplantation with further remission of the disease. Bone marrow transplantation increases overall survival and disease-free survival when compared to conventional treatment.
Conclusions: Since MM prognostic factors are numerous and, therefore, the understanding and analysis of the clinical and laboratory features of MM can contribute to an early diagnosis of patients, a targeted therapeutic approach and better outcomes.

Keywords: Multiple myeloma, Hematological malignancy, Bone involvement

INTRODUCTION

Multiple myeloma (MM) is an incurable however treatable hematologic malignancy in which plasmocytes (activated B lymphocytes) abnormally proliferate in bone marrow, usually resulting in an oversecretion of an antibody known as monoclonal immunoglobulin or monoclonal protein (M-protein), which can be easily measured in the blood or in urine.[1,2] Intensive plasmocyte growth in the bone marrow can crowd out normal blood-forming cells, leading to low blood cells counts and result in anemia, thrombocytopenia and leukopenia.[3,4] Thus, the patient could present tiredness and weakness, increased bleeding and bruising, along with impaired ability to a normal immune response. In addition, MM patients are usually affected by bone pain caused by the infiltration of

plasmocytes in the bones, accelerating the destruction of osteoblasts due to the production of an osteoclast-stimulating substance that can result in increased blood serum calcium levels (hypercalcemia) and cause fracture.[5] These lytic bone lesions occur in a majority (around 80%) of patients at diagnosis.[6] Furthermore, blood hyperviscosity and hypercalcemia can overload the kidney's physiological functions, leading to renal failure, another common clinical manifestation in these patients.[7] All of these clinical conditions can cause a substantial burden on patients and healthcare systems.[8]

Patients' clinical and laboratory conditions are determinant for MM diagnosis. According to the International Myeloma Working Group (IMWG), the diagnosis is confirmed if, at least, two features from three are present; excessive presence of neoplastic plasma cells in the bone marrow, usually quantified by bone marrow biopsy; presence of bone injuries or lytic bone lesions, detected by radiological exams, such as radiography, computed tomography, magnetic resonance and bone densitometry; excessive presence of immunoglobulin analyzed by serum protein electrophoresis (SPEP) or urine protein electrophoresis (UPEP) through immunofixation.[7,9-11] Additionally, other tests could be performed to confirm MM diagnosis, such as blood count (quantification of red blood cells, white blood cells and platelets), biochemical panel (quantification of serum calcium levels, creatinine, uric acid and liver enzymes), immunological panel (quantification of Kappa or Lambda light and free chains and IgA, IgG, IgM, IgE, IgD immunoglobulins).[12]

The initial stage of MM is called monoclonal gammopathy of undetermined significance (MGUS), characterized by the clonal expansion of transformed plasma cells, and it is underdiagnosed due to the asymptomatic condition and stability for several years. Disease progression to smoldering myeloma (SM) and MM is associated with numerous and increasingly damaging genetic alterations in clonal plasma cells, bone marrow infiltration and osteolytic bone lesions.[13] Thus, the IMWG has proposed the Revised International Staging System (RISS) in 2015 a new staging system based on the values of serum albumin, serum β2 microglobulin (β2M) and serum lactate dehydrogenase (LDH) and on cytogenetics, by fluorescent in situ hybridization, enabling the identification of del (17p), t (4;14) (p16;q32) or t (14;16) (q32;q23).[14,15] In patients in stage I, there are β2-microglobulin (β2M) levels lower than 3.5 mg/l, albumin levels up to 3.5 g/dl, standard-risk of chromosomal abnormalities, normal LDH and no organ damage.[16] Patients in higher risk (stage III) develop gene deletions associated with high LDH, end-organ damage and β2-microglobulin levels higher than 5.5 mg/l. In patients in stage II, the levels of β2-microglobulin and albumin are lower than 3.5 mg/l or β2-microglobulin levels are higher than 3.5 mg/l and albumin levers are lower than 5.5 g/dl.[17]

The evolution of myeloma is usually slow, but progressive, especially in the elderly (older than 65 years).[18] In order to provide better health conditions for these patients, palliative care is the option of choice and aggressive treatments are rarely used. The treatment is generally divided into specific, to treat the tumor mass of the myeloma, and supportive, which treats other clinical manifestations, as bone pain resulted from the neoplasm. Symptomatic patients under the age of 70 are classified as suitable for intensive chemotherapy, then, undergo several cycles of chemotherapy and, if necessary, are submitted to autologous stem cell transplantation. Conversely, patients over the age of 70 are classified as not suitable for intensive chemotherapy, so mild chemotherapy is performed with drugs as melfalan, dexamethasone, thalidomide or edalidomide, bortezomib or carfilzomib, to reach the plateau state, where the M-protein is stable. Then, treatment is interrupted and maintenance is performed with thalidomide or lenalidomide. If there is an increase in M-protein, a relapse condition, the allogeneic transplant or a new autologous stem cell transplant could be recommended for patients under the age of 50, in addition to chemotherapy.[19]

Considering the importance of multiple myeloma as a severe hematological malignancy, the present study was conducted to evaluate the prognostic factors of MM and analyze the bone involvement in patients enrolled at an important regional hospital in the state of São Paulo, southeastern Brazil, over a period of 5 years. We aimed at identifying the variables related to MM diagnosis and the development of bone lesions. The understanding on the prognostic factors of MM could be helpful to adjust the treatment options according to patients' conditions and, therefore, minimize the impact on the healthcare system.

METHODS

Study design

The current investigation is a retrospective study conducted in Hospital Universitário São Francisco of Bragança Paulista (São Paulo, Brazil), in accordance with the declaration of Helsinki. All patients with a confirmed diagnosis of multiple myeloma at any time of follow up between January 2013 and December 2018 were included. The diagnosis was confirmed in accordance with the IMWG guidelines. Disease stage at diagnosis was determined according to the International Staging System (ISS; I, II or III). Remission, progression, and relapse were defined according to standard IMWG criteria.

Laboratorial analysis

Laboratorial parameters were collected at the time of diagnosis and during the treatment, including hematological, biochemical and immunological analysis. Hematological data, as hemoglobin levels, platelet

number and white blood cells in venous blood, was analyzed by flow cytometry. Biochemical tests included serum total calcium and serum creatinine while immunological parameters analyzed were serum protein electrophoresis, quantification of immunoglobulin type and serum ß2 microglobulin value.

Clinical analysis

Clinical data included gender, ethnicity, age at the time of MM diagnosis, ISS stage, laboratorial records, radiological findings, bone lesion (osteoporosis, osteolytic lesions and/or skeletal destruction), number and types of therapies including chemo/radiotherapy, autologous stem cell transplantation (ASCT) for MM, response and overall survival (OS).

Statistics analysis

Statistical analyses were performed using GraphPad Prism5 software (CA, USA). Data were expressed as the number values (minimum-maximum) and percentage (%). For comparisons, an appropriate Mann-Whitney test was used considering the 95% confidence interval. The values of $p<0.05$ were considered statistically significant.

RESULTS

Patient population

In this retrospective study, we verified the medical records of 42 patients with a confirmed diagnosis of MM between 2013 and 2018. Most patients, 54.76% (23/42) were older than 65. Regarding patients' gender, males and females corresponded to 16 (38.10%) and 26 (61.90%), respectively. In relation to ethnics, most multiple myeloid patients were white (80.49%) (Table 1).

Clinical analysis

The main clinical manifestation observed in our patients was anemia in 61.90% (26/42), followed by bone involvement 59.52% (25/42), hypercreatinemia 26.19% (11/42) and hypercalcemia 14.29% (6/42). The presence of other neoplasms associated with Multiple Myeloma was observed in 9.91% (5/42) patients. Interestingly, 19.04 (8/42) did not present any symptom, including bone changes (Table 1).

Laboratorial analysis

We also analyzed the laboratory parameters associated with the main clinical manifestations. Since one the most common clinical manifestations reported about the patients with MM is usually anemia, we evaluated the hematological data. Most patients, 61.90% (26/42), presented hemoglobin levels below 12 mg/dl. Only 11.90% (5/42) patients had thrombocytopenia (platelet count lower than 140,000.00/mm^3) at diagnosis (Table 1).

Table 1: Clinical and laboratory characteristics of patients diagnosed with MM.

Parameters	N	%
Sociodemographic		
Age (years)		
≥65	19	45.24
<65	23	54.76
Gender		
Female	26	61.90
Male	16	38.10
Blood parameters		
Hemoglobin (<12.0 mg/dl)	26	61.90
Leucocytes (≥10200/mm^3)	5	11.90
Lymphocytes (≥3150/mm^3)	2	4.76
Platelets (<140,000/mm^3)	5	11.90
Biochemical parameters (mg/dl)		
Creatinine (>2.0)	9	21.42
Calcium (>10.2)	6	14.28
Urea (>50.0)	14	33.33
Beta 2 microglobulin (mcg/ml)		
< 3.5	13	30.95
>3.5 and <5.5	3	7.14
> 5.5	19	45.24
Not specified	7	16.67
Imunoglobulin chains		
IgA Kappa	6	14.29
IgA Lambda	4	9.52
IgG Kappa	13	30.95
IgG Lambda	3	7.14
Kappa only	7	16.67
Lambda only	5	11.90
Not specified	4	9.52
Stage		
I	13	30.95
II	3	7.14
III	19	45.24
Not specified	7	16.67

Due to the renal failure frequently found in patients diagnosed with MM, we analyzed the values of creatinine, calcium and urea in serum, which are associated with kidney damage when increased levels are observed. Interestingly, very high values of serum creatinine (greater than or equal to 2.00 mg/dl) were found in 21.42% (9/42) patients. The measurement of serum calcium levels showed that 54.76% (23/42) presented higher than 10.2 mg/dl. The dosage of urea showed 33.33% (14/42) patients with levels higher than 50 mg/dl (Table 1).

Stage of MM

For the assessment of the stage of MM, the main diagnostic criterion was based on the serum measurement of beta 2 microglobulin, a protein present in the cell membrane mainly of lymphocytes. In 39.95% (13/42) of

our patients, the quantification of beta 2 microglobulin was below 3.5 mcg/dl; in 7.14% (3/42), the beta 2 microglobulin values were above 3.5 mcg/dl and below 5.5 mcg/dl and in 45.24% (19/42), beta 2 microglobulin values were greater than 5.5 mcg/dl. Thus, using the classification of the international myeloma working group, most patients diagnosed with MM are in stage III of the disease, considered the most advanced (Table 1).

The types and subtypes of MM could also be determined by measuring the immunoglobulins produced by plasma cells. Immunoglobulins are composed of two heavy chains and two light chains, with five types of heavy protein chains, G, A, D, E and M, and two types of protein light chains, being kappa and lambda. Regarding the dosage of the light chain types, we observed that 14.29% (6/42) had Kappa IgA light chains, 30.95% (13/42) had Kappa IgG light chain, 16.67% (7/42), 9.52% (4/42) had Lambda IgA light chains, 7.14% (3/42) had light chains Lambda IgG, 11.90% (5/42) had isolated Lambda light chains. A percentage of 9.52 (4/42) were not specified (Table 1).

Radiological analysis

The imaging modalities used for the diagnosis to bone pain or fractures were X-ray 28.57% (12/42), CT 26.19% (11/42), PET-CT 9.52% (4/42) and MRI 7.14% (3/42). Most patients, 38.10% (16/42), presented one involved site, 14.29% (6/42) had two sites, and 4.76% (2/42) had three sites, while involvement in four was present in 2.38% (1/42) of patients. Among the 42 patients evaluated, the majority 59.52% (25/42) presented alterations on imaging exams, such as osteopenia, lytic lesions and fractures, with the vertebrae, skull, ribs, pelvis and proximal portion of the humerus and femur the places with greater commitment.

Regarding bone lesions, 28.57% (12/42) had lytic lesions, 14.29% (6/42) had fractures, 4.76% (2/42) had osteogenic lesions, 4.76% (2/42) had spondyloarthropathy, 4.76% (2/42) had osteoporosis and 2.38% (1/42) had bone demineralization (Table 2).

Treatment

The most commonly used treatment was combination chemotherapy with or without radiotherapy. Regarding treatment, all patients underwent chemotherapy, with 69.05% (29/42) using cyclophosphamide, dexamethasone and thalidomide (CTD) while 30.95% (13/42) used another type of chemotherapy.

Survival analyses and prognostic factors

At the end of the study, in December 2018, there were 73.80% (31/42) patients alive, 64.28% (27/42) undergoing medical treatment or monitoring and 11.90% (5/42) transplanted. The median of the overall survival of the 42 patients analyzed was 33.5 months, ranging from 11 days to 48.30 months. A percentage of 26.19% (11/42) patients died (Figure 1).

Table 2: Bone involvement features in patients diagnosed with MM.

Parameters	N	(%)
Imaging modalities		
X-ray	12	28.57
CT	11	26.19
PET-CT	4	9.52
MRI	3	7.14
Involved site		
1	16	38.10
2	6	14.29
3	2	4.76
4	1	2.38
Type of lesion		
Lytic lesions	12	28.57
Fracture	6	14.29
Osteogenic lesions	2	4.76
Spondyloarthropathy	2	4.76
Osteoporosis	2	4.76
Bone demineralization	1	2.38
Total	42	100.00

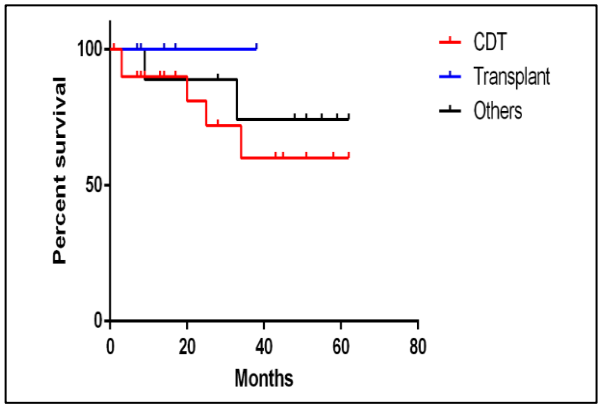

Figure 1: Kaplan-Meier survival curves of patients diagnosed with MM and treated with CDT, autologous transplant or other treatments. All patients submitted to transplantation survived, whereas survival of patients undergoing CDT treatment was significantly inferior.

DISCUSSION

In MM, the second most common hematological neoplasm, monoclonal plasma cells grow out of normal, usually with an extensive bone destruction (osteolytic lesions, osteopenia and/or fractures), bone marrow failure and accumulation of abnormal immunoglobulin, mainly in kidney.[1,19-21] Furthermore, MM patients had an increased infection risk since a multifactorial immunodeficiency, corresponding to one of the major causes of morbidity and mortality in this hematological

neoplasm.[22] The MM diagnosis is based on an increased numbers of immature and abnormal plasma cells in the bone marrow, the presence of a monoclonal protein in the serum or urine or osteolytic bone lesions.[23] After the confirmed diagnosis, the patient is classified into stages of disease I, II, or III and the treatment, isolated or association of drugs, is focus on stabilization, development, disease progression and improvement of the patient's life.[24] The cure is generally rare.

This research sought to identify patients diagnosed with MM, between 2013 to 2018, at hospital Universitário São Francisco (HUSF) and analyze the variables related to MM diagnosis and the development of bone lesions. During a five-year period, 42 medical records of patients diagnosed at hospital Universitário São Francisco, Bragança Paulista, São Paulo, Brazil, were analyzed. The average age of patients was over 60 years. Regarding gender, most of the patients evaluated in our study were female. Generally, a higher prevalence of MM is observed in males possibly due to male hormonal changes and a cumulative effect of environmental exposures related to the type of work performed, such as exposure to chemical substances, pollutants and radiation.[25]

In current study, we found that most patients (61.90%) had anemia, with hemoglobin levels below 12g/dl as well as bone pain, injury or bone fractures. After an analysis of imaging exams, considered the gold standard, most patients showed bone alterations, such as osteopenia, lytic lesions and fractures, with the vertebrae, skull, ribs, pelvis and proximal portion of the humerus and femur being the places with greater commitment. Lytic lesions and bone pain are results of infiltration of plasmocytes in the bone marrow, which causes an imbalance in the interaction between osteoclast and osteoblast and the plasmocytes adherence to the stroma, causing production of osteoclast, activating factors, suppression of osteogenesis and activation bone destruction.[26]

Lytic bone lesions are an important feature of multiple myeloma, in particular, because they cause pain and hypercalcemia, and lead to bone complications.[27] Elevated calcium levels, usually seen in patients with advanced MM, are associated with symptoms such as fatigue, confusion, weakness, vomiting, excessive urination, renal and neurological disorders, lethargy and coma. In the current study, high serum calcium values were observed in 14.28% of the patients, which may have contributed to renal failure. Other factors also contribute to the development of kidney failure, such as serum levels of creatinine and urea. Our analysis showed that high serum creatinine values in 21.42% of patients, indicating impairment of the kidney's filtration capacity. Tubular damage caused by immunoglobulins secreted by plasma cells could also cause obstruction and irreversible and progressive damage to the kidneys and, when associated with hypercalcemia, the kidneys increase their filtration rate culminating in recurrent injuries to the glomeruli.[21] Kidney impairment for patients diagnosed with MM is a serious complication to the prognosis of the disease, as it severely affects renal filtration. Thus, the patient with MM who has renal failure should be referred to the hemodialysis center to perform weekly blood filtration sessions mechanically. All patients diagnosed with MM who had renal failure underwent hemodialysis.

After the confirmed diagnosis of MM, the stage of this neoplasia was analyzed through the serum measurement of beta 2 microglobulin, which is a protein found on the surface of almost all cells of the body. In individuals affected with MM, this protein is increased at the serum or urinary level, since there is renal impairment and the filtration and reabsorption of beta 2 microglobulin does not occur effectively, being eliminated in the urine. In individuals affected by renal failure and undergoing dialysis, beta 2 microglobulin can form long protein chains that are deposited in joints and tissues, a condition called beta 2 microglobulin amyloidosis associated with dialysis, causing pain and stiffness in the deposited tissues. Analysis of serum beta 2 microglobulin levels showed that 45.24% patients had high levels of this globulin, indicating an advanced stage of the disease and consequently a less favorable prognosis for treatment as well as remission. In the majority of our patients, a secretion of IgG, the most common type was observed, followed by the secretion of IgA and IgM respectively. IgG myeloma characterizes the usual symptomatic of the pathology, while IgA myeloma can characterize tumors outside the bones and IgD myeloma may be accompanied by plasma cell leukemia.

Despite this staging, 64.28% of the patients evaluated are undergoing treatment or medical follow-up. Thus, the therapeutic choice was effective and has helped in the patients' better quality of life. In most cases evaluated, treatment was based on the administration of the drugs cyclophosphamide, dexamethasone and thalidomide (CTD), a potential combination for elderly patients diagnosed with Multiple myeloma. Cyclophosphamide is a cytostatic agent, which has the capacity to destroy malignant cells, dexamethasone is a corticosteroid that helps to reduce symptoms, such as nausea and vomiting, caused by chemotherapy, and thalidomide is an immunomodulator. Due to the synergism between these drugs, there is an increase in the overall response rate and in the remission rate. Interestingly, 11.90% patients underwent autologous bone marrow transplantation and presented a remission of the disease. Bone marrow transplantation increases overall survival and disease-free survival when compared to conventional treatment. However, most patients with MM are not eligible due to age and other associated comorbidities.[28] The purpose of therapy with autologous transplantation is to keep the patient without signs and symptoms of the disease for several years, it is considered a safe therapy, it does not usually cause adverse effects and it is indicated as a complementary form to chemotherapy. Regarding the survival curve evaluating the proposed treatment, bone

marrow transplantation was the most effective and significantly positive treatment because there was no death after the transplant. Although other chemotherapy drugs showed an intermediate survival rate and the joint therapy of cyclophosphamide, dexamethasone and thalidomine, inferior survival rates, both treatment options demonstrated validity as proposed therapy. Nonetheless, the findings of this study should be seen in light of some limitations, as the difficulty to replicate and the conclusions drawn from a particular group may not be totally transferable to other settings. Therefore, future research should be conducted in order to increase the number of patients and corroborate our findings.

CONCLUSION

In light of these findings, our study showed that most patients presented complications as part of the disease, mainly typical clinical manifestations of MM, such as anemia, bone pain and renal failure, as well as an advanced clinical stage at diagnosis. The better understanding and analysis of the clinical and laboratory manifestations of Multiple Myeloma can contribute to an early diagnosis of patients, assisting in providing medical attention and faster treatment.

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