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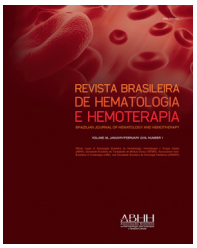

Original article

Multiple myeloma and central nervous system involvement: experience of a Brazilian center

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ABSTRACT

Introduction: The estimated involvement of the central nervous system in patients with multiple myeloma is rare at about 1%. The infiltration can be identified at the time multiple myeloma is diagnosed or during its progression. However, it is more common in refractory disease or during relapse.

Methods: This retrospective cohort study reviewed data from medical records of patients followed up at the Gammopathy Outpatient Clinic of *Santa Casa de Misericórdia de São Paulo* from January 2008 to December 2016.

Results: Twenty patients were included, with a median follow-up of 33.5 months after central nervous system infiltration. The prevalence was 7%. The median age at diagnosis of multiple myeloma was 56.1 years, with 70% of participants being female. Sixteen patients had central nervous system infiltration at diagnosis of multiple myeloma. Seventeen patients had exclusive osteodural lesions and three had infiltrations of the leptomeninge, of which one had exclusive involvement and two had associated osteodural lesions. The median overall survival was 40.3 months after central nervous system involvement. The median overall survival in the group with central nervous system infiltration at relapse was 7.4 months. The patients with leptomeningeal involvement had a median overall survival of 5.8 months.

Conclusion: Central nervous system infiltration is a rare condition, but it should be considered as a possibility in patients with multiple myeloma and neurological symptoms. The best treatment regimen for this condition remains unknown and, in most cases, the prognosis is unfavorable.

Introduction

Multiple myeloma (MM) is characterized by the clonal proliferation of plasma cells, which produce monoclonal immunoglobulins found in blood and/or urine.[1] Generally, these plasma cells are confined to the bone marrow and vascular compartment; however, dissemination may occur through the bone cortex or hematogenically to other organs, resulting in extramedullary disease.[2]

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Extramedullary involvement in MM is rare, occurring in only 3–5% of patients and usually involving the skin, nasopharynx, larynx, upper respiratory tract and central nervous system (CNS).[3] CNS involvement, estimated at 1% of patients, is uncommon.[4]

The definition of CNS involvement in MM is controversial and differs depending on the group of investigators. Such involvement may occur as single or multiple intraparenchymatous lesions and/or leptomeningeal involvement.[5] It is defined by the presence of plasma cells in the cerebrospinal fluid (CSF) and/or leptomeninge, dura mater or intraparenchymatous involvement as assessed by imaging tests and confirmed by CSF analysis, magnetic resonance imaging (MRI), computed tomography (CT) scans and/or tissue biopsy.[6,7]

The CNS involvement by MM confers a reserved prognosis, with an overall survival (OS) of around 1.5–2 months when there is leptomeningeal infiltration.[4–6] For those cases with osteodural involvement, the median survival ranges from one year to 25 months.[3,8]

The best treatment for MM with CNS involvement is not well defined yet. The therapies used are intrathecal chemotherapy, radiotherapy, and systemic therapy in addition to autologous hematopoietic progenitor cell transplantation (AHPCT).[6] These therapies can be used alone or as a combination.

In the present study, 20 patients with MM and CNS infiltration were evaluated with the objective of contributing to a better understanding of the biology, clinical behavior and their treatment, as well as to assess the OS. This is the largest Brazilian single-center study of patients with MM and CNS involvement.

Objectives

To evaluate the profile of patients diagnosed with MM and CNS involvement including the OS, and to correlate infiltration with predictive factors and prognostic impact.

Methods

This is a retrospective cohort study of patients with MM and CNS involvement followed up at the Gammopathy Outpatient Clinic of *Santa Casa de Misericórdia de São Paulo* from January 2008 to December 2016.

Initially, patients with CNS involvement during that period were identified in the database of the outpatient clinic and a review was carried out of their medical records in the institution's Medical and Statistical Archive Service.

Data regarding the clinical and demographic characteristics of the patients, their diagnosis of MM and CNS infiltration were collected, as well as data on treatment and response.

Inclusion and exclusion criteria

Patients diagnosed with MM with CNS involvement at the time of diagnosis or during progression were included in this study. CNS involvement was defined as having a dura mater lesion with contiguity to the CNS, isolated intraparenchymatous lesions, lesions starting from nasopharyngeal plasmacytoma and those with leptomeningeal involvement as detected by the presence of clonal plasma cells in the CSF and/or by imaging.

Patients were excluded when data in the medical records were incomplete making it impossible to confirm the diagnosis of CNS involvement.

Statistical analysis

Continuous variables were summarized by means of variation (minimum and maximum values), mean, standard deviation (SD), median and interquartile range. Categorical variables are described by means of absolute and relative frequencies. The Kolmogorov–Smirnov test was used to evaluate the distribution pattern of the numerical variables in the sample. Survival analyses were performed using the Kaplan–Meier technique and comparison across groups by the log-rank test. All analyses were performed using MedCalc software (Mariakerke, Belgium, V. 11.3.3.0). Two-tailed significance levels of 5% were used as indicative of statistical difference across groups.

Results

From January 2008 to December 2016, 285 patients with MM were followed up at the Gammopathy Outpatient Clinic at *Santa Casa de Misericórdia de São Paulo*. Of these cases, 21 were identified with CNS involvement, but one was excluded due to incomplete data in their medical record. Accordingly, 20 patients were eligible for the present study. These patients were diagnosed with MM between February 2002 and September 2015.

The median follow up of the patients since the diagnosis of MM was 38.5 months, while the median after CNS infiltration was 33.5 months.

The prevalence of patients with CNS involvement in the period studied was 7%.

Six (30%) patients were male and 14 (70%) were female. The median age at MM diagnosis was 56.1 years (range: 49.0–66.1 years) and at CNS involvement it was 57.0 years (range: 49.0–66.0 years).

The most frequent immunoglobulin heavy chain subtype was IgG (kappa and lambda – 9 cases) followed by IgA (kappa and lambda – 7 cases). Three patients had light chain disease (one kappa and two lambda).

At diagnosis of MM, two patients (10.5%) had Durie-Salmon stage IA, four (21%) had stage IIA and 13 (68.4%) had stage IIIA/B.

According to the International Staging System (ISS), seven patients (35.0%) had stage I, six (30.0%) had stage II and seven (35.0%) had stage III.

CNS involvement was identified in sixteen patients (80%) at MM diagnosis and in four (20%) during disease progression, of which one patient had a complete response (CR). The median interval between MM diagnosis and the diagnosis of CNS infiltration was 14.5 months (range: 6.1–20.3 – Table 1).

Lactate dehydrogenase (LDH) values were elevated in 36.8% of patients at MM diagnosis and elevated in 38.9% at the diagnosis of CNS infiltration.

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