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Research Article

Risk Stratification of Patients with Myelofibrosis in the HEMORIO: A Retrospective Study

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ABSTRACT

Background: Myelofibrosis patients may be classified into risk categories that were developed using a prognostic scoring system which includes several factors. The objective of this article is to obtain knowledge about the risk-classification distribution of myelofibrosis in a high complexity unit in the period of 2019.

Methods: This is an observational, descriptive and retrospective study with a quantitative approach in which 17 medical records of patients diagnosed with primary myelofibrosis were assessed.

Results: The average age at diagnosis was around the sixth and seventh decades of life. An improvement in the risk classification of the studied patients is observed, demonstrating a more effective treatment. In the evaluation of presence of constitutional symptoms the results have shown that four patients had weight loss, three had fever, seven had sweating, seven had fatigue, five had constant abdominal pain, six had pruritus and eight had some type of bone pain. No early satiety was reported by any patient.

Conclusions: Myelofibrosis patients monitored in the HEMORIO are mostly classified as intermediate risk individuals. Analyses of disease characteristics are essential for a better understanding and definition of strategies to its management.

Keywords: Primary myelofibrosis; Risk classification; Hematology

INTRODUCTION

Myelofibrosis is a disorder of the bone marrow consisting of an increasing fibrosis that occurs in the medullary tissue and affects the blood cells production. The disease is rare and occurs in five to ten people per million inhabitants, with a higher incidence in those over 65 years of age and a similar occurrence between men and women [1].

The myeloproliferative neoplasm term associated with myelofibrosis can refer to a new entity or be associated with the transformation of a polycythemia vera or essential thrombocythemia, hence the primary or secondary term. This disease is a clonal proliferation of the stem cell associated with a characteristic pattern in the stroma, and a leukoerythroblastic reaction and increase in inflammatory cytokines are observed in the peripheral blood [2]. The clinical manifestation varies, including progressive anemia, leukopenia or leukocytosis, thrombocytopenia or thrombocytosis and extramedullary hematopoiesis in some organs, but it commonly causes hepatomegaly and symptomatic splenomegaly. Patients with the advanced disease suffer from constitutional symptoms and giant splenomegaly (pain, splenic infarction, portal hypertension and dyspnea), in addition to progressive bone marrow failure, pulmonary hypertension and transformation to leukemia and death [3].

It is the most severe form among the myeloproliferative diseases (of which the most frequent are polycythemia vera and essential thrombocytosis), characterized by increased blood cell production, which leads to bone marrow fibrosis [4]. Most patients with myelofibrosis are symptomatic and have weight loss, fatigue, anemia, splenomegaly and increased inflammatory cytokines [5].

In recent years, new mutations in the MPL and JAK2 genes have been described, which allowed to expand the knowledge about the molecular bases of these diseases and thus improve their

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diagnostic and treatment capacity [4]. These findings resulted in the development of the targeted molecular therapy, namely the JAK2 inhibitors [5].

Extramedullary hematopoiesis is always present in the liver and spleen, contributing to the hepatosplenomegaly described in these patients. However, extramedullary hematopoiesis is rarely effective. Production foci can be found in the adrenal glands, kidneys, ganglia, bladder, breasts, lungs and other places [5]. When there is the presence of extramedullary hematopoiesis in the central nervous system, subdural hemorrhage, delirium, increased cerebrospinal fluid pressure, coma and several motor and sensory changes can be observed. Pleural and pericardial effusions can occur due to extramedullary production in serous membranes. After splenectomy, the hepatic hematopoiesis may worsen, leading to this organ insufficiency [6].

The factors used to classify patients into risk categories were developed using a prognostic scoring system that includes: age over 65 years, anemia/hemoglobin less than 10 g/dL, leukocytosis greater than 30,000/mm^3 or leukopenia less than 4,000/mm^3, circulating blasts greater than 1% and presence of constitutional symptoms such as weight loss, sweating, fever, fatigue, pruritus and abdominal pain [6]. The presence of one of the factors corresponds to a risk classification score: a score of 0 indicates low risk; a score of 1 corresponds to intermediate risk 1; a score of 2 indicates intermediate risk 2; and a score of 3 is equivalent to high risk [7]. The International Prognostic Scoring System (IPSS), applied at the time of the patient's diagnosis, and the Dynamic International Prognostic Scoring System (DIPSS) are tools that allow the patient to be evaluated according to this score [8].

Due to the lack of data from high complexity institutions in Rio de Janeiro that monitor this type of patient and with the aid provided by means of the classification at diagnosis of myelofibrosis, this work was conducted to determine the risk-classification distribution of HEMORIO patients using the IPSS and DIPSS tools, in addition to the assessment of age profiles and constitutional and fundamental symptoms for this type of classification.

METHODOLOGY

This is an observational, descriptive and retrospective study with a quantitative approach in which 17 medical records of patients diagnosed with primary myelofibrosis and enrolled in the HEMORIO were evaluated.

HEMORIO is the coordinator of the public blood network of the State of Rio de Janeiro, Brazil, responsible for collecting, processing and distributing blood bags to more than 120 health services that make up the Unified Health System (SUS) of the State of Rio de Janeiro [9]. It is a hematology and hemotherapy reference center in Rio de Janeiro and, within the SUS hierarchical network, a tertiary unit specialized in the treatment of highly complex primary hematological diseases. It provides health care for patients with primary hematological diseases on an outpatient and inpatient basis [9].

In the HEMORIO, the medical records are filed by pathology following diagnostic criteria from the institution's manual. In the case of myelofibrosis, all patients underwent bone biopsy, with diffuse fibrosis in the bone marrow and absence of Philadelphia chromosome and BCR-ABL. For this analysis, a convenience sample was considered and all patients diagnosed with the disease and enrolled in the institution in 2019 were included.

The risk factors were evaluated following the clinical evolution and tests performed at each outpatient visit, paid according to the patient's clinical status, which could be every 15 days, monthly or bimonthly. The first risk factor assessed was the presence of anemia (hemoglobin less than 10 g/dl), peripheral blasts (above 1%) in the white blood cell count (less than 4,000 or greater than 30,000/mm^3), and upon clinical examination the presence of splenomegaly. The period of this evaluation was from January 2019 until December 2019.

Based on these data, the risk stratification was performed using the IPSS that is applied to patients at the time of diagnosis and employs five parameters: age greater than 65 years, hemoglobin greater than 10 g/dl, leukocyte count greater than 25 × 10/l, circulating blasts greater or equal to 1% and presence of constitutional symptoms. The presence of 0, 1, 2 and 3 or more adverse factors defines the risk as low, intermediate 1, intermediate 2 and high 10. The development of the dynamic prognostic system (DIPSS) uses the same prognostic variables employed in the IPSS and can be applied at any time during the time of the disease. The patient's current state in 2019 was used as a parameter to carry out this classification and the IPSS considered the patient's state at the time of his enrollment in the HEMORIO [10].

The statistical analysis was quantitative and plotted on an Excel chart. The requirement of a signed informed consent form was waived because this is a retrospective study, without subjects' identification, of medical records, analyzed and approved by the HEMORIO scientific committee (Figure 1).

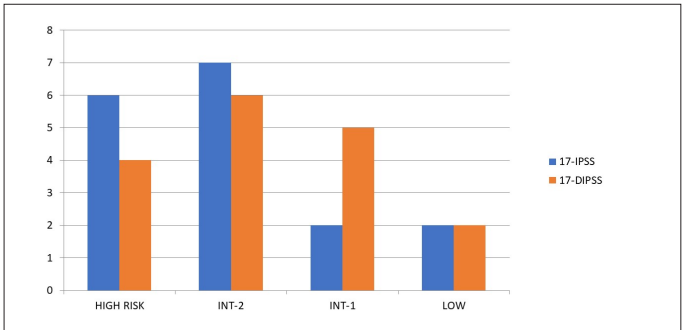

Figure 1: Risk classification of IPSS/DIPSS.

RESULTS

A total of 17 patients were included in the study sample. Of these, 7 were male and 10 female and only 3 patients were under 60 years of age (majority was>60 years old; n=14 patients). As for the treatment used, 7 patients were on hydroxyurea, 1 was on

danazol and erythropoietin, 2 underwent only red blood cell concentrate transfusion and 7 started ruxolitinib.

The follow-up period of these highly complex patients was 2 years, respecting 1 year for the DIPSS assessment of each one of them. Considering the risk stratification of primary myelofibrosis of the 17 patients according to the IPSS, the following frequency was observed: six were classified as high risk patients, seven as intermediate risk 2, two as intermediate risk 1 and two as low risk. According to the DIPSS in 2019, four patients were classified as high risk, six as intermediate risk 2, five as intermediate risk 1 and two as low risk as shown in Table 1.

Myelofibrosis patients	High risk	Int-2	Int-1	Low
17-IPSS	6	7	2	2
17-DIPSS	4	6	5	2

Abbreviations: INT-1: Intermediate 1, INT-2: Intermediate 2

Table 1: IPSS/DIPSS risk classification.

The following constitutional symptoms were observed throughout the analysis of medical records: weight loss, fever, sweating, fatigue, abdominal pain, pruritus, early satiety and bone pain. Of the twelve patients, four had weight loss; three had a fever; seven had sweating; seven had fatigue; five had constant abdominal pain; six had pruritus and eight had some type of bone pain. No early satiety was reported by any patient.

DISCUSSION

According to Eduardo Fagundes dos Santos' thesis (2015), acute myelofibrosis is a myeloproliferative disease with a patients' median age of 67 years and therefore greater prevalence in the third age, corroborating what we have observed in our study with 14 patients over 60 years of age and 3 patients under 60 years of age [11].

The survival of patients with acute myelofibrosis in several studies ranged from 27 months (2.3 years) to 135 months (11.3 years) after diagnosis, with a median survival of 5.7 years. Approximately 20% of patients develop acute leukemia in the first decade of the disease, whose survival after transformation was 2.6 months and represented the most frequent cause of death [11]. It is noteworthy that in our group no transformation to leukemia was observed, only a polycythemia vera that turned into myelofibrosis.

Concerning the risk classification of the 17 myelofibrosis patients, a percent improvement in the DIPSS compared to IPSS, with fewer high risk patients, is observed, and the increase in intermediate risk 1 versus intermediate risk 2 indicates an effective treatment, probably due to the use, in seven patients of this study with massive splenomegaly, of ruxolitinib that provided an improvement of over 50% in the size of the spleen, as well as relief of symptoms such as sweating, fatigue, weight loss and cachexia, demonstrating a significant increase in quality of life.

Myelofibrosis is a clonal manifestation with medullary fibrosis associated with osteosclerosis, angiogenesis and extramedullary hematopoiesis having its clinical evidence of severe anemia, hepatosplenomegaly, constitutional symptoms as fatigue, excessive sweating, fever, cachexia, bone pain, splenic infarction, pruritus, thrombosis and bleedings. None of the 17 studied patients showed any episode of bleeding, thrombosis, severe bone pain or signs of portal hypertension [10].

Despite its important contributions, this study has limitations. As main limitation, it is necessary to highlight the retrospective nature of the follow-up, which limits the quality of information to be described to that available in the medical record. In addition, the sample consists of a small number of patients from a single center in Rio de Janeiro and may not be representative of the reality of individuals with the condition in the country.

CONCLUSION

Based on the findings presented in this study, it is possible to conclude that myelofibrosis patients monitored in the HEMORIO are mostly classified as intermediate risk individuals, in addition to being over 60 years of age. As for constitutional symptoms, bone pain, sweating and fatigue were the most frequently observed. Considering that myelofibrosis is a very rare disease, the collection of this type of information is essential for a better understanding and definition of strategies to manage the disease.

CONFLICT OF INTEREST

None to report

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