Leukemia Research 63 (2017) 34–40

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

Symptom burden profile in myelofibrosis patients with thrombocytopenia: Lessons and unmet needs

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http://dx.doi.org/10.1016/j.leukres.2017.10.002
Received 8 July 2017; Received in revised form 7 October 2017; Accepted 11 October 2017
Available online 14 October 2017

ARTICLE INFO

Keywords:
Myeloproliferative neoplasm
Myelofibrosis
Thrombocytopenia
Quality of life
Symptomatology

ABSTRACT

Myelofibrosis is a myeloproliferative neoplasm associated with progressive cytopenias and high symptom burden. MF patients with thrombocytopenia have poor prognosis but the presence of thrombocytopenia frequently precludes the use of JAK2 inhibitors. In this study, we assessed quality of life and symptom burden in 418 MF patients with (n = 89) and without (n = 329) thrombocytopenia using prospective data from the MPN-QOL study group database, including the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) and Total Symptom Score (MPN10). Thrombocytopenia, defined as platelet count < 100×10^9/L (moderate 51–100×10^9/L; severe ≤50×10^9/L), was associated with anemia (76% vs. 45%, $p < 0.001$), leukopenia (29% vs. 11%, $p < 0.001$), and need for red blood cell transfusion (35% vs. 19%, $p = 0.002$). Thrombocytopenic patients had more fatigue, early satiety, inactivity, dizziness, sad mood, cough, night sweats, itching, fever, and weight loss; total symptom scores were also higher (33 vs. 24, $p < 0.001$). Patients with severe thrombocytopenia were more likely to have anemia (86% vs. 67%, $p = 0.04$), leukopenia (40% vs. 20%, $p = 0.04$), and transfusion requirements (51% vs. 20%, $p = 0.002$) but few differences in symptoms when compared to patients with moderate thrombocytopenia. These results suggest that MF patients with thrombocytopenia experience greater symptomatic burden than MF patients without thrombocytopenia and may benefit from additional therapies.

1. Introduction

Myelofibrosis (MF) is a clonally derived Philadelphia chromosome negative myeloproliferative neoplasm (MPN) associated with progressive cytopenias and potential to transform into acute myelogenous leukemia (AML). MPNs are often associated with dysregulated signaling of the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway. The most common somatic mutation, JAK2 V617F, occurs in 50–60% of patients with MF [1–3].

MF patients exhibit a high degree of symptomatology with potentially dramatic impacts on quality of life (QOL). Common symptoms include abdominal pain, bone pain, fatigue, pruritus, night sweats, fever, and weight loss [4]. Cytopenic derangements are common and closely linked to disease progression. In particular, thrombocytopenia is a proven negative prognostic indicator and predictor of transformation to AML [5]. MF patients with platelets under 50×10^9/L have more frequent anemia and leukopenia and higher rates of both hemorrhagic and thrombotic complications compared to MF patients with higher platelet counts [6].

Treatment options are limited for patients with thrombocytopenia. Ruxolitinib, a JAK1/JAK2 inhibitor, was shown in the phase III COMFORT-I [7] and COMFORT-II [8] trials to have significant symptomatic benefit in intermediate-2 or high risk MF patients with platelets of at least 100×10^9/L. However, the drug may paradoxically contribute to thrombocytopenia and is presently only indicated in patients with platelets of at least 50×10^9/L.

To date, no investigation has evaluated the correlations between patient symptomatology and platelet count. In this study, we aimed to characterize the symptom burden in MF patients with and without thrombocytopenia using prospectively collected quality of life data. We also assessed differences in clinical characteristics and symptomatology among patients with varying degrees of thrombocytopenia.

2. Methods

2.1. Patient selection

This study was approved by the Institutional Review Board (IRB) of the Mayo Clinic. Data were prospectively collected from an international pool of MPN patients recruited from academic, private practice, and government-funded centers. A total of 418 patients were included in the study; all had a diagnosis of MF. Patients completed the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF), Brief Fatigue Inventory (BFI), and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) via self-reporting. All surveys were completed in the patients' native language (English, German, Dutch, French, Spanish, Italian, Chinese, and Swedish) and translated to English using standard PRO translational methods. Clinical information was also gathered at the time of survey collection and included laboratory information, treatment history, prognostic scoring, and physical examination results as assessed by clinicians.

In this study, thrombocytopenia was defined as a platelet count less than 100×10^9/L, anemia was defined as hemoglobin less than 11 g/dL, and leukopenia was defined as a white blood cell (WBC) count less than 3.5×10^9/L. Moderate thrombocytopenia was defined as a platelet count of 51–100×10^9/L, and severe thrombocytopenia was defined as a platelet count less than or equal to 50×10^9/L. A broader categorization of patients with "lab abnormality" included any patient who met criteria for anemia, leukopenia, or thrombocytopenia.

2.2. Symptom evaluation

Symptom evaluation was performed using the previously validated MPN-SAF [9]. All participants were required to complete at least six of the ten MPN-SAF symptom questions to meet study inclusion criteria. Symptoms were scored on a scale from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be), and items specifically assessed quality of life (QOL), early satiety, abdominal pain or discomfort, inactivity, headache, difficulty with concentration, dizziness, numbness, insomnia, sad mood, difficulty with sexual desire or function, cough, night sweats, itching, bone pain, fever, and weight loss. Total symptom score (TSS) was calculated by multiplying the average score across items by ten to achieve a 0–100 scaled score. The MD Anderson BFI was used to assess worst fatigue rating [10]. Splenomegaly was assessed by clinicians based on physical examination and reported as an estimated value in centimeters.

2.3. Prognostic scoring

The Dynamic International Prognostic Scoring System (DIPSS) was used to calculate MF prognostic scores [11]. Patients were stratified into low risk (0 points), intermediate-1 risk (1–2 points), intermediate-2 risk (3–4 points), and high risk (> 4 points) using the following scoring variables: circulating blasts greater than or equal to 1% (1 point), constitutional symptoms (1 point), age greater than 65 years (1 point), WBC count greater than or equal to 25×10^9/L (1 point), and hemoglobin less than 11 g/dL (2 points).