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Review

Allogeneic Stem Cell Transplantation in Myelofibrosis

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A B S T R A C T

Myeloproliferative neoplasm (MPN) is a category in the World Health Organization classification of myeloid tumors. *BCR-ABL1*–negative MPN is a subcategory that includes primary myelofibrosis (MF), post–essential thrombocythemia MF, and post–polycythemia vera MF. These disorders are characterized by stem cell–derived clonal myeloproliferation. Clinically, these diseases present with anemia and splenomegaly and significant constitutional symptoms such as severe fatigue, symptoms associated with an enlarged spleen and liver, pruritus, fevers, night sweats, and bone pain. Multiple treatment options may provide symptom relief and improved survival; however, allogeneic stem cell transplantation (HCT) remains the only potentially curative option. The decision for a transplant is based on patient prognosis, age, comorbidities, and functional status. This review describes the recent data on various peritransplantation factors and their effect on outcomes of patients with MF and new therapeutic areas, such as the use and timing of Janus kinase inhibitors with HCT and gives overall conclusions from the available data in the published literature.

INTRODUCTION

Myelofibrosis (MF) is a clonal myeloproliferative neoplasm (MPN) that can arise de novo or result from previous polycythemia vera or essential thrombocythemia (post-ET MF). MF is characterized by a clonal stem cell process, resulting in ineffective erythropoiesis, reactive fibrosis in bone marrow, and extramedullary hematopoiesis in the spleen or in multiple organs [1]. The disease process causes debilitating symptoms as a consequence of anemia and splenomegaly, leading to fatigue, abdominal discomfort, early satiety, cachexia, constitutional symptoms, and eventually death. Reported causes of death include transformation to acute leukemia, progression of primary disease, thrombosis and cardiovascular complications, and infection or bleeding [2]. Herein, we discuss prognostic factors; current therapeutic options, including nonallogeneic stem cell transplant and allogeneic stem cell transplant (HCT); pre-HCT factors; and post-HCT factors. Future directions and some ongoing studies are also discussed. A PubMed search was conducted, using the keywords "myelofibrosis," "allogeneic stem cell transplantation" and "Janus kinase (JAK) inhibitors." Published abstracts related to the search were also reviewed.

Symptom Burden

Patients with MF can have a significant symptom burden, which can include severe fatigue, symptoms associated with an enlarged spleen and liver, pruritus, fevers, night sweats, and bone pain. To quantify the symptoms associated with MF, the Myelofibrosis Symptom Assessment Form (SAF) was created in 2009 [3]. This survey asks a series of 20 questions, and patients rate their symptom score on a scale of 0 to 10, with 0 being "not a problem" and 10 being "the worst imaginable symptom." In 2011, this survey was expanded to become the 27-question Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF), created to encompass MF as well as polycythemia vera and ET [4]. This form included assessment of microvascular symptoms, such as insomnia, difficulty concentrating, sexual dysfunction, vertigo, headaches, and numbness/tingling. The MPN-SAF was subsequently consolidated into a 10-question survey known as the MPN-SAF-Total Symptoms Scale (MPN-SAF-TSS), which captured relevant data in a shorter format [5]. A clinical response is indicated by a 50% reduction in the total score. The current guidelines recommend collecting the MPN-SAF for the initial evaluation and MPN-SAF-TSS for subsequent follow-up assessments [6].

Prognostic Factors

Clinical prognostic scoring systems

The median survival of patients with MF varies from 1.5 years to more than a decade, depending on the severity of disease. Multiple scoring systems have been used over the

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years to guide patients and providers in treatment choices. The International Prognostic Scoring System (IPSS) uses age over 65 years, presence of constitutional symptoms, hemoglobin less than 10 g/dL, WBC count greater than 25×10.9/L, and circulating blasts over 1% as risk factors for determining survival [2]. Using this system, median survival in patients with low risk (0 risk factors) was 135 months; intermediate-1 risk (1 risk factor), 95 months; intermediate-2 risk (2 risk factors), 48 months; and high risk (≥3 risk factors), 27 months.

In 2010 the Dynamic IPSS (DIPSS) was developed. This prognostic model could be used to guide decision-making at any time during the clinical course of primary MF [7]. Median survival of patients with low risk (score of 0) was not reached; for intermediate-1 risk (score of 1 or 2), median survival was 14.2 years; for intermediate-2 risk (score of 3 or 4), 4 years; and for high risk (score of 5 or 6), 1.5 years. In addition to the DIPSS variables as predictors of overall survival in primary MF, DIPSS plus included patients with an unfavorable karyotype, a platelet count less than 100×10^9/L, and a need for RBC transfusion [8]. An additional point was assigned to each of these additional variables. Unfavorable karyotype included a complex karyotype or 1 or 2 abnormalities, including +8, –7/7q-, i(17q), –5/5q-, 12p-, inv(3), or 11q23 rearrangement.

Driver mutations

Driver mutations, such as those in *JAK2*, myeloproliferative leukemia receptor (*MPL*) and calreticulin receptor (*CAL-R*), have been shown to be associated with poor survival and leukemic transformation. These mutations are crucial for decision-making because they substantially affect disease biology and outcomes. Primary MF with triple-negative mutation status (ie, negative for *JAK2*, *MPL,* or *CAL-R* mutations) has a poorer prognosis and higher risk of leukemic transformation. Data from patients at the Mayo Clinic Rochester were used to estimate overall survival from the date of diagnosis or first referral and showed a median overall survival of 4.3 years for patients with *JAK2* mutant, 4.1 years for patients with *MPL* mutant, 8.2 years for patients with *CAL-R* mutant, and 2.5 years for patients with a triple-negative mutation [9]. In an Italian study the estimated overall median survival from time of diagnosis was 9.2 years for patients with *JAK2* mutant, 9.1 years for patients with *MPL* mutant, 17.7 years for patients with *CAL-R* mutant, and 3.2 years for patients with a triple-negative mutation [10]. The *CAL-R* mutation was shown to have a relatively indolent course compared with the *JAK2* mutation in ET and primary MF.

Other somatic mutations

Somatic mutations other than *JAK2*, *MPL,* and *CAL-R* are frequently observed by next-generation sequencing in patients with MF. Mutations such as *ASXL1, SRSF2,* and *EZH2* mutations independently and negatively affect survival, whereas *IDH1/2*, *SRSF2*, and *ASXL1* mutations were associated with leukemic transformation [11]. Also, patients with *CAL-R* unmutated and *ASXL1* mutant (*CAL-R–/ASXL+*) primary MF had a particularly poor survival (median, 2.3 years) [9]. Next-generation sequencing in 189 patients identified variants in *SCRIB, MIR662, BARD1, TCF12, FAT4, DAP3, POLG*, and *NRAS,* which were recurrent and occurred in more than 3% of patients with MPN who were tested [12]. In addition, 8 patients (4.7%) in this study with primary MF who harbored a heterozygous *NRAS* mutation in codon 12 had a poorer prognosis and were associated with a higher risk category (intermediate-2 and higher).

Additional somatic mutations are being identified. These mutations may add to the current scoring systems and may identify patients in the intermediate-risk or low-risk categories who have a greater chance of disease progression. For these patients an HCT would be considered earlier in their treatment course. The Mutation-Enhanced IPSS (MIPSS) has more recently been described and includes mutations such as *JAK2, MPL, CAL-R, EZH2, ASXL1, IDH1/2*, and *SRSF2* [13]. In this scoring system age over 60 years, constitutional symptoms, hemoglobin level less than 10 g/dL, platelet count less than 200×10^9/L, triple-negative mutation status, *JAK2* or *MPL* mutation, and *ASXL1* or *SRSF2* mutations were found to be significant risk factors for poor survival.

CURRENT THERAPEUTIC OPTIONS

Current treatment recommendations are based on the risk stratification from the DIPSS or DIPSS plus score and on the patient's symptom burden (Figure 1) [6]. The available pharmacologic therapies for MF are aimed at improving symptoms, quality of life, and overall survival. HCT remains the only potentially curative treatment modality for patients with MF [14].

Nontransplantation Options

Patients in low-risk and intermediate-1 risk categories can be observed for disease progression or given erythropoietin or hydroxyurea. For patients with an erythropoietin level less than 500 mU/mL, erythropoietin-stimulating agents may ameliorate the anemia [15]. IFN-α, pegylated IFN-alfa-2a, and pegylated iIFN-alfa-2b have also been evaluated in several series of patients with MF and have been shown to improve cellularity, splenomegaly, and bone marrow morphology [16-18].

Role of JAK *inhibitors*

Ruxolitinib is a selective *JAK1/JAK2* inhibitor approved by the US Food and Drug Administration in 2011 for intermediate- and high-risk MF patients, including those with primary MF, post–polycythemia vera MF, and post-ET MF. The US Food and Drug Administration approval was based on improvement in spleen size and quality of life in patients taking the drug compared with those given placebo and was the best available therapy in 2 phase III studies: COMFORT-I and COMFORT-II (Controlled Myelofibrosis Study With Oral *JAK* Inhibitor) [19,20]. The COMFORT studies included patients with intermediate-2 and high-risk disease. In the 3-year follow-up to COMFORT-II, there was a survival advantage with the use of ruxolitinib [21]. The most commonly reported hematologic adverse effects in the COMFORT studies were anemia and thrombocytopenia, which improved after prolonged therapy beyond 8 to 12 weeks. Retrospective data also show a benefit for ruxolitinib in symptomatic patients with low-risk disease [22]. The ROBUST trial included patients with intermediate-1, intermediate-2, and high-risk MF, with improvement noted in the symptom score in approximately 80% of patients with intermediate-1 risk disease [23]. The role and efficacy in patients with low-risk MF is yet to be evaluated in a prospective trial. Recently published National Comprehensive Cancer Network guidelines recommend its use in intermediate- and high-risk disease and recommend consideration of use in patients who are symptomatic with low-risk disease [6].

Other *JAK2* inhibitors being developed that have shown promising early results are pacritinib and momelotinib. Pacritinib is a *JAK2/FLT-3* inhibitor that is better tolerated in