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Janus Kinase Inhibitors and Stem Cell Transplantation in Myelofibrosis

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Abstract

Myelofibrosis (MF) is characterized by splenomegaly, blood count abnormalities, particularly cytopenias, and a propensity for transformation to acute leukemia. The current treatment approach is to ameliorate symptoms due to these abnormalities. Treatment with Janus kinase 2 inhibitors reduces spleen size and improves symptoms in patients with MF, but most of the patients eventually have disease progression and stop responding. Allogeneic stem cell transplantation remains the only curative option. However, its efficacy must be balanced against the risk of treatment-related death and long-term sequelae of transplant like chronic graft versus host disease. The challenge is to integrate treatment with Janus kinase inhibitors with allogeneic stem cell transplantation.

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Introduction

Myelofibrosis (MF) is an uncommon disease, with an estimated incidence of 0.5-15 cases per 100,000 individuals, and the median patient age at presentation of 67 years. The clinical course of MF is heterogeneous, ranging from an indolent disease in some patients, who might survive for decades, to an aggressive disease in others, often associated with disabling constitutional symptoms, poor quality of life, and survival durations measured in months. The disease can appear de novo (primary MF) or after a previously known case of polycythemia vera (PV) or essential thrombocythemia (ET) (post-PV MF and post-ET MF, respectively),[1] but its clinical and histological characteristics and prognosis are essentially the same in either scenario. Palliative modalities used in MF patients include erythropoietin, androgens, immunomodulatory agents, interferon, cytoreductive therapies, and nonpharmacological approaches, such as blood transfusion, splenic irradiation, and splenectomy. The only potentially curative therapy for MF is allogeneic stem cell transplantation (ASCT). Because MF is primarily a disease of the elderly and often complicated by disabling constitutional symptoms, transplantation can be challenging. However, with the advent of reduced intensity conditioning regimens, the applicability of ASCT has broadened to include a larger proportion of MF patients.[2] The availability of Janus kinase *(JAK) 1/2* inhibitors has allowed clinicians to provide symptom relief and improve quality of life in MF patients. The availability of these drugs might also affect decision-making regarding the timing of ASCT. Future research should address the role of treatment with *JAK1/2* inhibitors in MF patients who are transplantation candidates and determine their role in the context of transplantation, which might lead to new therapeutic strategies for MF.

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Pathogenesis

Myelofibrosis is caused by clonal proliferation of hematopoietic progenitors,[3,4] which release fibrogenic cytokines, leading to bone marrow fibrosis. A major manifestation of MF is extramedullary hematopoiesis in organs such as the spleen and the liver,[5] resulting in enlargement of these organs. The discovery of the *V617F* mutation of the *JAK2* gene[6] represented important progress in understanding the pathogenesis of MF and paved the way for molecularly targeted therapy for MF with JAK inhibitors. Authors subsequently described other mutations, as well.[7,8] *V617F* mutation of the *JAK2* gene is present in 60% of patients with primary myelofibrosis (PMF) and post-ET MF and 95% of those with post-PV MF. This mutation results in a gain of function (ie, constitutive activation of the *JAK/STAT* pathway) that plays an important role in the proliferation, differentiation, and survival of hemopoietic cells. Researchers also have shown that patients with *JAK2*-negative myeloproliferative neoplasms (MPNs) have dysregulated *JAK/STAT* signaling[9] and that the *JAK/STAT* pathway is overactive even in patients who do not have this mutation. Therefore, although the available evidence indicates that *JAK2* mutation might not be the

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first molecular event in the pathogenesis of MPNs,[9] the *JAK/STAT* pathway is an attractive drug target. More recently, authors described new mutations involving the calreticulin (*CALR*) gene in patients with PMF and ET.[10,11] *CALR* mutations were mutually exclusive from *JAK2* mutations in those studies. These data suggest that patients with PMF who harbor the *CALR* mutation have superior survival over those with *JAK2* mutations.[10] Investigators have observed additional mutations that occur in patients with other myeloid neoplasias in a low proportion of MF patients. Some of these mutations, such as *Casitas B-lineage Lymphoma* and *lymphocyte-specific adaptator protein* mutations, result in loss of function, whereas others, including ten–eleven translocation, oncogene family member 2, ASXL1 (Additional sex combs-like 1), and *EZH2* (Enhancer of zeste homolog 2) mutations, affect proteins involved in epigenetic regulation of transcription.[9,12] Researchers used the latter findings as a basis for considering epigenetics as a possible therapeutic target for MF.[13] Mutations of genes encoding for different components of the RNA splicing machinery, such as *splicing factor 3b 1* and *SRSF2* (serine/arginine-rich splicing factor 2), also occur in MF patients.[14] In addition, a minority of patients with PMF or post-ET MF, most of whom are negative for the JAK2 mutation, harbor the *JAK/STAT*-activating *MPL* (Myeloproliferative leukemia virus) mutation of the thrombopoietin receptor gene.[7] Overall, these new insights into the molecular pathogenesis of MF might lead to the availability of improved drugs for the treatment of the disease and a different transplantation landscape.

Prognosis and Risk Stratification

Because of the marked heterogeneity of the clinical course of MF, a risk-adapted approach is essential to guide therapeutic decision-making. MF also affects a heterogeneous patient group and is often associated with frequent comorbidities and disease-related complications and a number of transplantation challenges related to patient selection, timing, and choice of conditioning regimen (Figure 1).

At present, the International Prognostic Scoring System (IPSS) is the most widely used approach for risk stratification of MF.[15] A dynamic IPSS (DIPSS) score was developed using the same 5 variables in IPSS (age $>$ 65 years, presence of constitutional symptoms [weight loss $>$ 10% of the baseline value in the year preceding diagnosis and/or unexplained fever or excessive sweating persisting for $>$ 1 month], hemoglobin level $<$ 10 g/dL [100 g/L], leukocyte count $>$ 25 $\times$ 10^9/L, and $\geq$ 1% circulating blasts) but enables prediction of prognosis at any time during the course of PMF.[16] The DIPSS was subsequently refined to the DIPSS plus, which includes 3 additional independent risk factors: transfusion dependence, unfavorable karyotype,[17] and platelet count $<$ 100.[18] According to the DIPSS plus, low-risk patients (0 adverse points) have a median survival duration of approximately 185 months. Intermediate-1 risk patients (1 adverse point) have a median survival duration of approximately 78 months. Intermediate-2 risk patients (2 or 3 adverse points) have a median survival duration of approximately 35 months. Finally, high-risk patients (4-6 adverse points) have a median survival duration of approximately 16 months.

All of these prognostic scoring systems are based on analyses of patients with PMF, not secondary MF. Further refinement of risk stratification systems is expected with the integration of somatic mutations into the models. A recent study demonstrated the *ASXL1, SRSF2, IDH1/2 (Isocytrate Dehydrogenase 1 and 2)*, and *EZH2* mutations to be independently associated with poor

Figure 1 Factors to Consider in Making Decisions About Allogeneic Stem Cell Transplantation for Myelofibrosis