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Review

Janus Kinase Inhibitors and Allogeneic Stem Cell Transplantation for Myelofibrosis

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A B S T R A C T

Myelofibrosis (MF) is a manifestation of several disorders of hematopoiesis, collectively referred to as myeloproliferative neoplasms. Allogeneic hematopoietic stem cell transplantation (ASCT) is the only therapy with proven curative potential. However, most patients with MF are in their 6th or 7th decade of life, and only some of these patients have been considered suitable transplantation candidates. The development of reduced-intensity conditioning regimens with limited toxicity has allowed clinicians to offer ASCT to a growing number of older patients. The availability of Janus Kinase (JAK) 1/2 inhibitors allows clinicians to provide symptom relief and improved quality of life for MF patients. These drugs may also affect the decision regarding, in particular, the timing of ASCT. Future studies need to address the role of JAK1/2 inhibitors in patients who are transplantation candidates and determine their role before and, possibly, after transplantation. The identification of indications for the use of JAK1/2 inhibitors in the context of transplantation may lead to new therapeutic strategies for patients with MF.

INTRODUCTION

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) characterized by expansion of clonal hematopoietic cells and the release of cytokines that trigger the development of marrow fibrosis, neoangiogenesis, and osteosclerosis. PMF manifests with blood cytopenias, leukoerythroblastosis, extramedullary hematopoiesis, and progressive splenomegaly that may be accompanied by hepatomegaly. PMF is a rare disorder, with an estimated annual incidence of approximately 1 per 100,000 and prevalence of 4 to 6 per 100,000 persons [1]. The disease primarily affects older individuals (median age at presentation, 67 years). The course of the disease varies considerably, ranging from indolent, with survival of more than a decade, to aggressive, with disabling constitutional symptoms, impaired quality of life, cachexia, and death within a year or 2 [2]. Myelofibrosis (MF) can also arise from polycythemia vera (PPV-MF) and essential thrombocythemia (PET-MF). Although the phenotypes may be similar to that of PMF, PPV-MF and PET-MF represent distinct clinical entities [3].

Conventional therapies, such as erythropoietin, androgens, immunomodulatory drugs, interferon-alpha, cytoreductive agents, and nonpharmacological options, such as blood transfusion, spleen irradiation, and splenectomy, have not significantly prolonged patient survival. Allogeneic stem cell transplantation (ASCT) is the only currently available therapy with curative potential for MF [4]. However, because MF mainly affects older individuals, most MF patients have traditionally not been considered for ASCT. With the more recent adoption of reduced-intensity conditioning (RIC) regimens, ASCT has become applicable to a larger proportion of patients with MF [5-9]. However, in older individuals, comorbidities (related or unrelated to MF) are common and may create challenges even with RIC, further affecting patient selection for ASCT, transplantation timing, and conditioning strategy [10,11]. Data on how the use of Janus Kinase (JAK) 1/2 inhibitors will impact transplantation outcomes are only beginning to emerge [12-14].

RISK-SCORING AND PATIENT SELECTION

Therapeutic decisions surrounding ASCT for MF require a risk-adapted approach. The Lille score, based on hemoglobin

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level and white blood cell count, has been used to guide risk-adapted therapy, suggesting that ASCT should be considered with intermediate- or higher risk disease (1 or 2 risk factors) [15]. More recently, new scoring systems have been developed.

The International Prognostic Scoring System (IPSS) estimates the expected survival from the time of MF diagnosis based on 5 risk factors [16]: (1) age > 65 years, (2) hemoglobin < 100 g/L, (3) leukocyte count > 25 × 10^9/L, (4) circulating myeloblasts ≥ 1%, and (5) presence of constitutional symptoms.

In the IPSS, patients are classified as low risk (score = 0, median survival of 135 months), intermediate-1 risk (score = 1, median survival of 95 months), intermediate-2 risk (score = 2, median survival of 48 months), or high risk (score ≥ 3, median survival of 27 months) [16]. A dynamic IPSS (DIPSS) score, proposed subsequently, uses the same 5 risk factors but allows for prognostic prediction at any time during the disease course. Under the DIPSS, hemoglobin concentration <100 g/L received a score of 2 points; the overall classification is as follows [17]: low risk is indicated by a score of 0; intermediate-1 risk, score of 1 or 2; intermediate-2 risk, score of 3 or 4; and high risk, score of 5 or 6.

The DIPSS has been further refined as DIPSS Plus, which adds 3 additional risk factors—transfusion dependence, unfavorable karyotype, and platelet count < 100 × 10^9/L—each assigned a 1-point score [18]. All of these scoring systems were based on studies in patients with PMF only and were developed before the wider availability of JAK inhibitors.

Further refinement of risk stratification systems is expected by integrating somatic mutations in the models. One recent study has shown *ASXL1*, *SRSF2*, *IDH1/2*, and *EZH2* mutations to be independently associated with poor survival [19]. Using the mutation information of these 4 genes, a follow-up study by the same investigators showed that the hazard ratios for survival were 2.78 and 1.52 for patients who had ≥ 2 mutations or 1 mutation, respectively, compared with patients without mutations [20]. Recently, additional mutations involving the calreticulin (*CALR*) gene have been described in patients with PMF and essential thrombocythemia [21,22]. *CALR* mutations were mutually exclusive from mutations in *JAK2*. The data suggest that patients with PMF who harbor a *CALR* mutation have superior survival compared with those with a *JAK2* mutation [21]. It is not known at present how the presence of *ASLX1*, *SRSF2*, *IDH1/2*, and *EZH2* mutations in *CALR*-positive patients may affect prognosis.

FACTORS AFFECTING TRANSPLANTATION PROGNOSIS

Additional factors that may affect outcomes after ASCT include the presence of comorbidities, stem cell donor type, and conditioning regimen [2,11,23-25]. Because patient comorbidities weigh heavily in transplantation decisions, additional (not disease-specific) scoring systems have been developed, in particular the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI). This index assigns weighted scores to particular medical conditions that affect nonrelapse mortality and survival. The highest scores are assigned to heart valve disease, severely impaired pulmonary function, moderate-to-severe hepatic disease, and a history of a solid tumor malignancy [23]. Although a formal validation in MF patients is pending, 2 recent analyses of transplantation results in patients with MF showed an inverse correlation of HCT-CI scores and transplantation success [26,27].

The prognostic value of the Lille scoring system has been studied extensively in hematopoietic cell transplantation (HCT) recipients [1,4]. Although patients with low-risk disease have better outcomes compared with those of intermediate- and high-risk patients, these patients are generally not considered candidates for transplantation, as their survival with supportive therapy alone is usually good. Relapse incidence appears to be higher in patients with high Lille scores [11]. Studies on the use of new scoring systems in predicting outcomes after HCT have not shown consistent results. Two studies reported that post-HCT success was dependent on pre-HCT DIPSS scores [26,27]; a large proportion of those patients received high-intensity (myeloablative) conditioning. Two large studies from the European Group for Blood and Marrow Transplantation and the Center for International Blood and Marrow Transplant Research (CIBMTR), focusing mainly on RIC, reported that DIPSS, although predictive, did not sufficiently differentiate between intermediate-1 and intermediate-2 risk populations [9,28].

It has been controversial whether splenectomy before transplantation is associated with better outcomes, although several studies have shown that hematopoietic recovery is faster in splenectomized patients. A recent study from the CIBMTR failed to show any impact of splenectomy or splenic radiation on graft-versus-host disease (GVHD) or survival in patients with myeloid malignancies, including myelofibrosis [29].

THE CHALLENGE OF ADVANCED AGE AND ASCT

One important factor in the decision-making process about transplantation is the advanced age of many patients with MF [2]. One retrospective study analyzed the results of ASCT in 30 patients, ages 60 to 78 years, with PMF, PPV-MF, or PET-MF, some with high HCT-CI scores [7]. Donors were human leukocyte antigen (HLA)–identical siblings or unrelated, and conditioning regimens ranged from very low (fludarabine plus 2 Gy total body irradiation) to high intensity (high-dose busulfan plus cyclophosphamide). With a median follow-up of 22 months, 3-year overall survival and progression-free survival were projected to be 45% and 40%, respectively. These results suggested that selected older patients with advanced MF can be treated successfully with ASCT.

ASCT AND DONOR SOURCES

Only 25% to 30% of patients have an HLA-identical sibling, and increasing numbers of transplantations are carried out from unrelated donors (URD). Transplantations from HLA-mismatched related (haploidentical) donors or with umbilical cord blood (UCB) are also being explored in MF [30,31]. Several studies have reported results with URDs to be similar to those with HLA-identical siblings (outcomes with HLA-mismatched donors were inferior) [4,32]. However, data from the CIBMTR, showed a 1-year nonrelapse mortality of 27% for transplants from related donors and 43% for URD ASCT [33]. These data were confirmed by a recent update from the CIBMTR that showed adjusted probabilities of 5-year survival for matched sibling donors, well-matched URDs, and partially matched URDs after RIC of 56%, 48%, and 34%, respectively [9].

The Italian registry also showed lower transplantation-related mortality (TRM) with transplantations from related