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Allogeneic Stem Cell Transplant vs. Janus Kinase Inhibition in the Treatment of Primary Myelofibrosis or Myelofibrosis After Essential Thrombocythemia or Polycythemia Vera

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Abstract

Primary myelofibrosis is one of the Philadelphia chromosome–negative myeloproliferative neoplasms and is the member of that group with the worst survival and the most significant limitations in quality of life. Hepatosplenomegaly due to extramedullary hematopoiesis, constitutional symptoms, and cytopenias are the main manifestations. The natural history is highly variable, and up to 30% of patients can experience acceleration to acute myelogenous leukemia. Conventional therapy is only palliative and not always effective. However, huge advances have been achieved in the past 2 decades toward a better understanding of the pathogenesis of this disease, as well as improved management. Powerful risk stratification systems are now available and can reliably separate the patients into different prognostic categories to aid clinical management. Allogeneic stem cell transplant can offer cure but is still not universally applicable owing to the treatment-related mortality and toxicity. Nevertheless, outcomes of transplant are improving, owing to the introduction of reduced-intensity conditioning regimens and the optimization of remission monitoring techniques and relapse prevention strategies. The discovery of the V617F mutation of *JAK2* (Janus kinase 2) and some other molecular aberrations has shed more light on the molecular pathogenesis of the disease and has led to the introduction of novel therapies such as JAK2 inhibitors. In fact, JAK inhibitors have shown promising symptomatic efficacy, and the JAK inhibitor ruxolitinib has also shown a potential survival benefit. Future effort should be made to combine allogeneic stem cell transplant with JAK inhibition.

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Introduction

The term *myelofibrosis* (MF) alone usually refers to primary myelofibrosis (PMF), which is a stem cell–derived hematologic disorder characterized by a clonal proliferation of multiple cell types, especially the megakaryocytes. PMF is one of the Philadelphia chromosome–negative (Ph^-) myeloproliferative neoplasms (MPNs) and is the member of that group with the worst survival and the most significant limitations in quality of life. This proliferation is accompanied by an increased secretion of different cytokines with a secondary intramedullary fibrosis, osteosclerosis, angiogenesis, and extramedullary hematopoiesis.[1] Additionally, MF may develop as a late evolution of 2 other MPNs: polycythemia vera (post-PV MF) and essential thrombocythemia (post-ET MF).[2] The life expectancy of patients with PMF is variable, and the median survival is 69 months (95% CI, 61-76). Causes of death are transformation to acute leukemia (31%), progression without acute transformation (19%), thrombosis and cardiovascular complications (14%), infection (10%), bleeding (5%), portal hypertension (4%), and other causes (14%).[3] That study[3] established the International Prognostic Scoring System (IPSS) for PMF, which uses 5 prognostic variables: age $>$ 65 years, constitutional symptoms, hemoglobin $<$ 100 g/L, leukocyte count $>$ 25 $\times$ 10^9 cells/L, and the presence of circulating blasts. Median survival in the low-risk category (no risk factors) was 135 months; in the intermediate-1 risk category (1 risk factor), 95 months; in the intermediate-2 risk category (2 risk factors), 48 months; and in the high-risk category (3 or more risk factors), 27 months. The IPSS is a

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powerful risk stratification tool to estimate the life expectancy of patients with PMF at diagnosis. To track change of prognosis due to acquisition of new risk factors over time, the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) introduced the dynamic IPSS (DIPSS),[4] which includes the same variables used in the IPSS but applies more weight on the acquisition of anemia. Recently, several other IPSS independent risk factors such as unfavorable cytogenetic status (+8, −7/7q−, i(17q), inv(3), −5/5q−, 12p−, or 11q23 rearrangement; median survival, approximately 40 months)[5] and transfusion dependency (median survival, approximately 20 months)[6] were identified and combined with DIPSS to result in the DIPSSplus stratification system.[7] The systems are being increasingly implemented in daily practice to advise patients with PMF about their individualized risk status and to guide therapy decisions. More recently, molecular mutation can also be used as a prognostic model for survival.[8] PMF can be cured with successful allogeneic stem cell transplant (allo-SCT),[9] although the applicability of allo-SCT is limited owing to treatment-related mortality.

Conventional therapies for PMF/MF include the use of growth factors such as erythropoietin, androgens, immunomodulatory drugs, interferon alfa, cytoreductive agents, and nonpharmacologic options such as blood transfusion, spleen irradiation, and splenectomy. None of these approaches have been found to prolong survival.

The V617F mutation of *JAK2* (Janus kinase 2) is an acquired point mutation in the pseudokinase domain of the gene that confers a constitutive JAK2 pathway activation with resulting growth factor–independent proliferation of myeloid precursors.[10,11]

JAK inhibitors are compounds developed for the treatment of MPNs. Ruxolitinib is the first JAK inhibitor approved by the US Food and Drug Administration for use in patients with intermediate- or high-risk MF (primary MF, post-PV MF, post-ET MF) and in Europe for symptomatic patients with MF with splenomegaly, regardless of the IPSS risk classification. Ruxolitinib, a JAK1/JAK2 inhibitor, showed early and sustained clinical benefits in patients with intermediate-2 and high-risk MF, including spleen size reduction and improvement of constitutional symptoms in a phase I/II trial (INCB18424-251) and the phase III trials COMFORT-I and COMFORT-II (Controlled Myelofibrosis Study with Oral JAK Inhibitor Therapy).[12-14] A survival benefit with ruxolitinib was found in the COMFORT-I analysis, in a 3-year follow-up of the COMFORT-II study,[15,16] and (more recently) according to DIPSS.[17]

Allo-SCT for MF

The published experience in allo-SCT for MF is summarized in Table 1. In the late 1980s and early 1990s, the feasibility of allo-SCT for MF was confirmed in small studies.[18,19] One multicenter European-American report was published in the late 1990s and described a retrospective study with a larger cohort in which allo-SCT was performed using myeloablative conditioning (MAC) in relatively young patients (median age, 42 years). Nonrelapse mortality (NRM) was 27%, and the incidence of graft failure was 9%. The median overall survival (OS) and progression-free survival (PFS) reached 47% and 39%, respectively, at 5 years.[20] Another important study, from the Fred Hutchinson Cancer Research Center (Seattle, WA), was first published in 2003 and was updated 5 years later to include 104 patients, most of whom received allo-SCT after MAC. In this study, NRM at 5 years of 34% and OS at 7 years of 61% were reported.[9,21] A total-body irradiation–based study resulted in a high-risk NRM of 48% and a 2-year OS of 41%.[22]

Because MF is principally a disease of the elderly, the need was urgent to improve the tolerability of allo-SCT and enable more patients with advanced age to benefit from this treatment modality. The evidence of graft versus leukemia effect was already available through documented responses to donor lymphocyte infusion (DLI) after failure of allo-SCT.[23,24] This justified the use of the reduced-intensity conditioning (RIC) in the setting of allo-SCT for MF. Small pilot reports could confirm that RIC can reduce NRM without jeopardizing engraftment.[25-28] Larger clinical trials were published thereafter, but the only prospective study with a large sample size was conducted by the European Society for Blood and Marrow Transplantation (EBMT) and published in 2009 after including 103 patients. The median age was 55 years, and the NRM at 1 year was only 16%. The cumulative incidence of relapse was 22% at 3 years. PFS and OS at 5 years were 51% and 67%, respectively. Advanced age and HLA-mismatched donor were independent predictive factors for reduced OS.[29] The study was updated recently after a median follow-up of 60 months and published in abstract form. The 8-year OS was 65%, with a stable plateau after 5.3 years of follow-up. The 5-year disease-free survival was 40%, and the 5-year cumulative incidence of relapse/progression was 28%, with 3-year NRM of 21%.[30] Other studies using RIC or MAC confirmed the curative effect of allo-SCT irrespectively of the intensity of the conditioning regimen.[31-41] It could be speculated that reduction of NRM achieved using RIC regimens may be offset by the theoretically increased risk of relapse. Unfortunately, there is no prospective comparison to date between MAC and RIC in PMF. However, a retrospective comparison found no statistically significant difference in outcome or relapse incidence.[36] On the other hand, the efficacy of relapse prevention and treatment has improved in recent years owing to the use of minimal residual disease (MRD) monitoring strategies. Using sensitive assays to monitor *JAK2* V617F mutation (detectable in 60% of patients with MPNs) after allo-SCT, MRD and molecular relapse could be treated early using DLIs in lower doses resulting in no or less severe graft-versus-host disease.[42] Recently, more mutations and molecular markers such as *MPL* (myeloproliferative leukemia proto-oncogene, thrombopoietin receptor) W515L/K, TET2 (tet methylcytosine dioxygenase 2), ASXL1 (additional sex combs like transcriptional regulator 1), or CALR (calreticulin) could be discovered in Ph^- MPNs.[43-45] The possibility to use those markers for MRD analysis in MF should be elucidated in future studies.

According to the recently published recommendations of the European LeukemiaNet (ELN), it seems justified to offer allo-SCT to eligible patients with PMF whose median survival is expected to be less than 5 years. This includes patients with intermediate-2 and high risk according to IPSS, as well as those with transfusion dependency or unfavorable cytogenetic status.[46] Eligible patients with post-PV or post-ET MF are offered allo-SCT generally at the time of fibrotic transformation. Overall, there is an increase in the number of transplants in the United States and Europe, mainly