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EDITORIAL

Allogeneic hematopoietic cell transplantation versus drugs in myelofibrosis: the risk-benefit balancing act

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Primary myelofibrosis (PMF) is a chronic myeloid malignancy characterized by stem cell-derived clonal myeloproliferation, anemia, marked hepatosplenomegaly and other consequences of extramedullary hematopoiesis, constitutional symptoms, cachexia, peripheral blood leukoerythroblastosis, bone marrow fibrosis and osteosclerosis. The disease is associated with shortened survival (median ~69 months)[1] and causes of death include progression into blast phase disease. A subset of patients with either polycythemia vera (PV) or essential thrombocythemia (ET) progress into a clinical phenotype that is similar to PMF and such post-PV or post-ET MF is managed like PMF.

The International Prognostic Scoring System (IPSS) for PMF uses five independent predictors of inferior survival (age >65 years, hemoglobin <10 g/100 ml, leukocyte count $>25 \times 10^9$/l, circulating blasts ⩾1% and presence of constitutional symptoms) to stratify patients into low, intermediate-1, intermediate-2 and high-risk categories based on the presence of 0, 1, 2 or ⩾3 risk factors, respectively; the corresponding median survivals are estimated at 135, 95, 48, and 27 months.[1] More recently, red blood cell transfusion requirement at diagnosis (median survival ~20 months)[2] and the presence of 'unfavorable' cytogenetic abnormalities (median survival ~40 months)[3] were reported to carry an IPSS-independent adverse prognostic effect.

Conventional drug therapy in PMF has not been shown to prolong survival and only occasionally results in histological remission.[4] Therefore, such therapy is often used only when needed and specifically to improve symptomatic anemia or reduce spleen size. Drugs used in the former instance include androgen preparations, prednisone, erythropoiesis stimulating agents, danazol, thalidomide and lenalidomide;[5] each of these is associated with a response rate of 10–25% and response duration of 6–18 months. Unmaintained remissions are rare. Hydroxyurea is the current drug of choice for reducing spleen size and is also used to control marked leukocytosis or thrombocytosis. Splenectomy is an effective treatment option for drug-refractory symptomatic splenomegaly and may also abolish red blood cell transfusion dependency in approximately 25% of patients with transfusion-dependent anemia.[5] Radiation therapy is most useful in the treatment of non-hepatosplenic extramedullary hematopoiesis whereas splenic irradiation offers only transient benefit and might be associated with severe myelosuppression.[5]

Several investigational drugs are currently being evaluated in symptomatic patients with PMF and post-PV/ET MF. In a recent phase 2 randomized study,[6] oral pomalidomide (a second generation thalidomide analog) alone or with a tapering dose of prednisone resulted in anemia response rates of up to 36%; there was little benefit in terms of splenomegaly. At the effective dose level of 0.5 mg per day, the drug did not cause either neuropathy or severe myelosuppression. Recent descriptions of *JAK2*, *MPL* and *TET2* mutations in PMF and related myeloproliferative neoplasms have raised the prospect of molecularly targeted therapy.[7–9] Accordingly, the safety and efficacy of several anti-JAK2 drugs are currently being evaluated in PMF and post-PV/ET MF.[10] TG101348 is a potent and selective orally bioavailable JAK2 inhibitor with excellent *in vitro*[11] and *in vivo*[12] activity against *JAK2*V617F-driven proliferation. Preliminary results in humans suggest favorable effects on splenomegaly, leukocytosis and constitutional symptoms.[5] Similar treatment effects have also been shown with another JAK2/JAK1 inhibitor, INCB018424.[5] Other drugs that are currently in clinical trials or soon will be include both ATP mimetics (XL019, CYT387, AZD1480, SB1518) and histone deacetylase inhibitors (ITF2357, MK0683, LBH589).[5]

Hence, where does allogeneic hematopoietic cell transplantation (allo-HCT) fit into all this? Allo-HCT is currently the only treatment approach in MF that is potentially curative;[13] a substantial number of patients who survive allo-HCT experience complete hematological, histological and molecular remissions.[14] However, such therapy is complicated by relatively high treatment-related mortality and morbidity. During a recent review of the literature,[15] the estimated 1-year treatment-related mortality associated with conventional intensity conditioning (CIC) allo-HCT averaged about 30% and overall survival 50%. In the current issue of *Bone Marrow Transplantation*, Bacigalupo *et al.*[16] report a similar outcome (5-year median survival of 45%) for reduced intensity conditioning (RIC) allo-HCT in PMF; treatment-related and relapse-related death rates were each 41%. By comparison, in a recent study of non-transplanted but transplant-eligible patients (high- or intermediate-risk patients; age <60 years) with PMF, the 1- and 3-year survival rates ranged from 71 to 95% and 55 to 77%, respectively.[15] Furthermore, it should be noted that approximately 60% of patients undergoing allo-HCT experience extensive, treatment-requiring chronic graft-versus-host disease.[13]

Considering the above, how does one choose first between allo-HCT and drugs and subsequently between CIC and RIC allo-HCT for the treatment of patients with

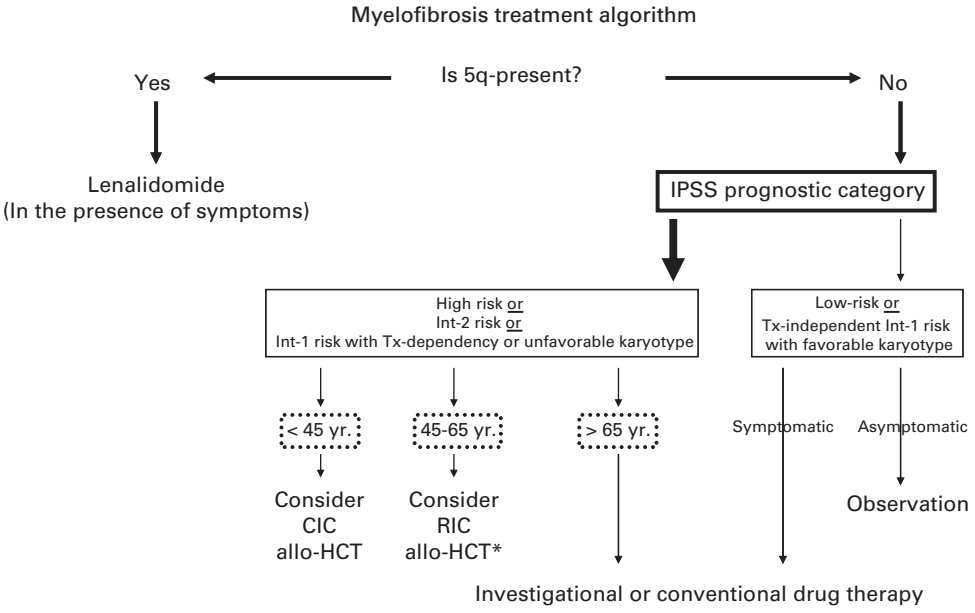

Figure 1 A treatment approach for the symptomatic patient with myelofibrosis. Key: IPSS, International Prognostic Scoring System for primary myelofibrosis; CIC, conventional intensity conditioning; RIC, reduced intensity conditioning; allo-HCT, allogeneic hematopoietic cell transplantation; Tx, red blood cell transfusion; Int, intermediate-risk. *Alternatively, one could consider investigational drug therapy in the presence of risk factors for poor transplant outcome (for example, presence of marked splenomegaly or absence of an HLA-identical sibling donor).

MF? In the absence of controlled studies, one has to rely on information from well-conducted retrospective and prospective cohort studies, such as those discussed above. In general, it is reasonable to justify the risk of allo-HCT-related complications in otherwise transplant-eligible patients whose median survival is expected to be less than 5 years (Figure 1). This would include IPSS high (median survival ~27 months) or intermediate-2 (median survival ~48 months) risk patients as well as those with either red blood cell transfusion need (median survival ~20 months)[2] or unfavorable cytogenetic abnormalities (median survival ~40 months).[17] However, not all such patients stand to benefit from allo-HCT. For example, in the aforementioned study concerning RIC allo-HCT, Bacigalupo *et al.*[16] reported a dismal 8% 5-year post-transplant survival rate for patients who displayed at least two of the following: red blood cell transfusion load of >20 units, splenomegaly that measures >22 cm by ultrasound, and use of a non-HLA-identical sibling donor. In another large study of primarily CIC allo-HCT,[13] risk factors for inferior post-transplant survival included increased HCT-specific comorbidity index[18] and advanced age. Taken together, these observations add another dimension to the transplant decision-making process that extends beyond the simplified approach illustrated in Figure 1, especially in light of the availability of clinical trials that offer novel drugs that might be effective in the setting of both marked splenomegaly (for example, JAK2 inhibitors) and anemia (for example, pomalidomide).

Finally, the study by Bacigalupo *et al.* provides some evidence that supports the use of pre-transplant splenectomy, in the setting of RIC allo-HCT, with the goal of improving survival for patients with large spleen. In contrast, splenectomy might not affect overall outcome for patients receiving CIC allo-HCT.[13] Regardless, preliminary results from currently ongoing JAK2 inhibitor clinical trials in MF indicate marked activity in reducing spleen size and suggest the potential use of such drugs in a pre-transplant setting.[5]

Conflict of interest

The author declares no conflict of interest.

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