Myeloproliferative neoplasms - Section 3

Stem cell transplantation in myelofibrosis

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Take Home Messages
- Allogeneic stem cell transplantation can cure patients with myelofibrosis by inducing molecular remission and complete resolution of bone marrow fibrosis.
- Because of the inherent complication of the procedure a careful selection of patients according to disease and transplant-specific risk factors is mandatory.

Patient selection
Patients with primary or post-essential thrombocytopenia/polycythemia vera myelofibrosis have a median survival of approximately 6 years but survival varies between from less than 2 to more than 15 years. Risk scores such as IPSS, dynamic IPSS (DIPSS), or DIPSS plus are currently used in clinical practice to determine the prognosis of patients with PMF. More recently molecular markers have been introduced into the PMF risk score and a specific score for post ET/PV myelofibrosis has been proposed. In the absence of data from prospective randomized studies, allogeneic stem cell transplantation is currently recommended for patients less than 70 years with an estimated median survival of less than 5 years. This would include patients with IPSS or DIPSS intermediate-2 and high risk and is based on a comparison between transplanted and non-transplanted patients in the pre-ruxolitinib era. In a recent expert consensus paper there was a recommendation to consider allogeneic SCT in intermediate-1 patients if other high risk features such as ASXL1 mutation, more than 2% peripheral blasts, refractory transfusion-dependent anemia, or adverse cytogenetics according to DIPSS plus, are present.

Transplant-specific risk factors
While disease-specific factors or scores influence the outcome after allogeneic stem cell transplantation, transplant-specific risk factors such as donor source or CMV-seropositivity and patient-specific factors such as age or comorbidities also affect outcome and should also be considered. In most of the transplant studies the use of alternative donors is associated with a worse outcome independent of disease-specific risk factors. Furthermore, not all disease-specific risk factors are currently considered as risk factors for outcome after allogeneic stem cell transplantation. For example, although ASXL1 mutations are also associated with a high risk of relapse after stem cell transplantation, the reported poor impact of CALR type 2 mutations has not been observed after allogeneic stem cell transplantation. The intensity of the conditioning regimen has not been tested prospectively but retrospective comparisons of myeloablative and reduced intensity preparative regimens resulted in similar outcome. Because of the reduced toxicity and generally older age of patients reduced-intensity conditioning regimens are currently used more frequently and account for about two-thirds of allotransplants for myelofibrosis reported to the EBMT registry. Regarding the donor, several studies reported worse outcome for mismatched or mismatched unrelated donors in comparison to HLA-identical siblings. Cord blood resulted in a high risk of graft failure. Haplo-identical donor with post-transplantation cyclophosphamide as GVHD prophylaxis is currently under investigation but more recent EBMT data reported a 5-year survival of only 38%.

Patient-specific risk factors
The most striking patient-specific risk factor for outcome after allogeneic stem cell transplantation is age. This is of note because myelofibrosis is a disease of elderly with a median age at disease of about 65 years. The impact of age is seen after myeloablative as well as after reduced intensity conditioning. Beside age, comorbidities and geriatric assessments also impact on outcome after allogeneic stem cell transplantation but have not been studied in myelofibrosis patients to date.

Role of splenectomy and JAK-inhibition
Splenomegaly is a hallmark of myelofibrosis and may have an impact on engraftment after stem cell transplantation. To reduce spleen size prior to transplantation some centers recommend splenectomy but morbidity can be high and mortality has been reported. The impact of splenectomy on outcome, especially on relapse, has been reported with contradictory results. Spleen irradiation to reduce spleen size has been reported successfully in single cases prior to conditioning. The available literature from the pre-ruxolitinib era suggests that splenectomy prior to transplantation could be beneficial. Since ruxolitinib is approved for symptomatic myelofibrosis several investigators have used ruxolitinib prior to transplantation to improve constitutional symptoms and to reduce spleen size. The European
LeukemiaNet and the European Society for Blood and Marrow Transplantation recommend the use of ruxolitinib at least 2 months prior to transplantation and a careful weaning prior to conditioning to avoid the rebound phenomenon. Of note, such strategy is currently evaluated in the prospective JAK A LLO study (NCT01795677). More recent data suggest better outcome after SCT if patients received transplant after responding to ruxolitinib rather than postponing the transplant until ruxolitinib failure.

Molecular remission and regression of bone marrow fibrosis

Since about 90% of myelofibrosis patients harbor one of the driver mutations JAK2V617F, calreticulin (CALR), or MPL, these mutations can be easily followed in peripheral blood by highly sensitive qPCR or digital PCR to determine molecular remission. No achievement of molecular remission on day 180 post allograft is associated with a significant higher incidence of a subsequent clinical relapse and may be used to guide adoptive immunotherapy with donor lymphocytes. Notably, bone marrow fibrosis as another hallmark of the disease, regresses rapidly after allogeneic SCT suggesting that fibrogenesis is a highly dynamic process. Systematic investigations have shown that about 60% of the patients have a complete or nearly complete remission of bone marrow fibrosis on day+100 and the percentage of patients increased to 90% at day+180.

Future perspectives

Allogeneic stem cell transplantation has become a standard curative treatment procedure for patients with advanced myelofibrosis. The annual numbers of transplants reported to the EBMT have steadily increased from 150 in 2003 to nearly 600 in 2015 and better characterization of disease-, patient-, and transplant-related risk factors may allow better selection of patients and timing of allogeneic stem cell transplantation (Figure 1). Defining the role of haplo-identical SCT as well as of JAK inhibitors treatment prior and during transplantation, and preventing relapse, the most frequent cause of treatment failure, by molecular monitoring and adoptive immunotherapy post transplantation, are the major challenges to be solved.

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