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REVIEW

JAK-2 inhibitors and allogeneic transplant in myelofibrosis

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SUMMARY

The activation of the JAK1/JAK2 pathway plays a crucial role in the pathogenesis of myelofibrosis. Treatment with the JAK2 inhibitor ruxolitinib demonstrated to reduce splenomegaly and symptoms in patients affected by myelofibrosis, leading to a significant improvement of overall survival in comparison with the supportive therapies. Taking in account this recent therapeutic progress, it is necessary to redefine the role of the allogeneic hematopoietic stem cell transplantation, which has been considered the only curative option for fit myelofibrosis patients up to now. In the era of JAK2 inhibitors, allogeneic transplant is still indicated in patients with intermediate-2 and high-risk myelofibrosis or red blood cell transfusion dependent patients or patients with unfavourable karyotype. There is no direct evidence to recommend which conditioning regimen should be preferentially adopted. Graft failure, relapse and transplant related mortality are still current issues of the allogeneic stem cell transplantation, particularly from unrelated donors. Ruxolitinib can be efficaciously included in the platform of allogeneic transplant. In fact, ruxolitinib treatment for 3-4 months before transplant has demonstrated to reduce spleen and improve performance status in about 30-50% of patients, without impairing the outcome of the subsequent transplant. Ruxolitinib has to stopped the day before conditioning to avoid rebound phenomenon. There are no sufficient data to recommend ruxolitinib administration after transplant with the aim of eradicating minimal residual disease and preventing relapse.

Key words: myelofibrosis, allogeneic hematopoietic stem cell transplantation, JAK-2 inhibitors, conditioning regimens.

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INTRODUCTION

Myelofibrosis (MF) is one of the classical BCR-ABL negative chronic myeloproliferative neoplasms (MPN), a group also including essential thrombocythemia (ET), and polycythemia vera (PV). The term MF is comprehensive of idiopathic or primary myelofibrosis, the most frequent form, PV-related MF and ET-related MF, with a similar presentation and clinical course (1,2). The disease is characterized by a clonal proliferation of a pluripotent stem cell associated

with an abnormal release of several cytokines and growth factors which lead to fibrosis, osteosclerosis, angiogenesis and extramedullary hematopoiesis associated with hepatosplenomegaly (3). The *JAK2V617F* mutation is found in 97% of patients affected by PV and in 60% of those affected by ET and MF. The JAK2 protein has a tyrosine kinase activity and the gain of function *V617F* mutation determines constitutional activation of the JAK/STAT pathway. The mutation in the thrombopoietin receptor gene (MPL) is reported in 8% of patients with MF. To underline the importance of the genetic component, in 2008 the World Health Organization (WHO) released the new diagnostic criteria for MF including the presence of these mutations in the major ones (4). Another crucial discovery was made in the 2013, when the somatic mutation of *CALR*, the gene encoding for calreticulin, was found in 20 to 25% of patients with ET or MF. Subsequently, several gene mutations including *CBL, LNK, TET2, ASXL1, IDH1, IDH2* and *IKZF* have been reported in MPNs (2).

CLINICAL FEATURES

The disease affects mainly elderly people with a median age at diagnosis of 65 years, men and women in equal percentage, but young people are not necessarily spared (1). Clinical manifestations are heterogeneous: at diagnosis nearly 30% of patients can be asymptomatic. The most common symptoms include severe anemia, constitutional symptoms (e.g. fatigue, night sweat and fever), bone pain, aquagenic pruritus and marked splenomegaly causing abdominal pain and early satiety. Portal and pulmonary hypertension can be observed (3, 4). The median overall survival (OS) of MF is nowadays ranges from 2 to 15 years (1). The main causes of death are infections, hemorrhage complications due to bone marrow (BM) failure, the evolution of the MF into acute leukemia, which can be observed in the 20% of the patients, and other complications linked to portal hypertension (5).

PROGNOSTIC SCORES

Since 2009 the International Prognostic Scoring System (IPSS) has been adopted: it is applicable at the presentation of the disease and identifies for risk categories: low, intermediate-1, intermediate-2 and high, based on five clinical features which are: age >65 years, hemoglobin <10g/dL, leukocyte count >25x10^9 /L, circulating blasts >1% and constitutional symptoms, assigning them one point each. The corresponding median OS per each category is 11.3, 7.9, 4 and 2.3 years.

The International Working Group for Myelofibrosis Research and Treatment (IWGMR) subsequently developed a dynamic prognostic model named DIPSS, that uses the same predictors, but it can be applied at any time during the disease course, and assigns two, instead of one adverse point, to the lower level of hemoglobin. Later, three other independent factors were added to the DIPPS: the presence of unfavorable karyotype (e.g.+8, −7/7q-, i(17q), −5/5q-, 12p-, inv(3) or 11q23 rearrangement), the need of red cell transfusion and the platelets count <100x10^9/L, leading to the DIPSS-PLUS (*Table 1*) (6-8).

The gene mutations are not included in the prognostic scores, but several stud-

TABLE 1 • Prognostic score systems.

	IPSS(6)	DIPSS(7)	DIPSS-PLUS(8)
Variables	• Age>65y • Hb <10 gr/dL • Leukocyte count >25x109/L • Blasts>1% • Constitutional symptoms	• Age >65y • Hb <10 gr/dL • Leukocyte count >25x109/L • Blasts >1% • Constitutional symptoms	• Age >65y • Hb <10 gr/dL • Leukocyte count >25x109/L • Blasts >1% • Constitutional symptoms • Platelets count <100x109/L • RBC transfusion need • Unfavorable karyotype*
Score	1 point each	1 point each Hb: 2 points	1 point each
Risk	Low 0 Intermediate-1 1 Intermediate-2 2 High 3	Low 0 Intermediate-1 1-2 Intermediate-2 3-4 High 5-6	Low 0 Intermediate-1 1 Intermediate-2 2-3 High 4-6

*unfavorable karyotype (e.g.+8, −7/7q-, i(17q), −5/5q-, 12p-, inv(3) or 11q23 rearrangement.

ies have been underlined their prognostic impact. The triple negative association (*JAK2, MPL* and *CALR*) predicts poor diagnosis, while isolated *CALR* mutation in combination with favorable clinical variables (higher platelets count, lower circulating leukocytes, higher hemoglobin level) seems to be linked with better prognosis (9, 10).

TREATMENT

Conventional treatment

Therapy for MF is conventionally based on the patient risk category, age and presenting disease manifestations. Before the introduction of JAK2 inhibitors, MF treatment was mainly palliative and was focused to improve clinical symptoms, for example hydrossiurea or busulfan for leukocytosis and danazol or thalidomide for anemia.

Ruxolitinib, an oral potent and selective JAK1/JAK2 tyrosine kinase inhibitor, was approved by FDA in 2011 and by EMA in 2012 the treatment of intermediate and high risk MF. It prevents activation of JAK-STAT signaling pathway and acts by reducing proliferation of MNP clone and by releasing inflammatory molecules (2).

Two randomized studies comparing ruxolitinib with placebo or best available therapy (BAT) have been published. In the COMFORT-I, a randomized, double blind phase 3 study, ruxolitinib was compared with placebo. The spleen volume reduction of 35% or more after 24 weeks was gained by 41.9% of patients in the ruxolitinib group and 0.7% in the placebo group. About 46% of patients who received ruxolitinib experienced an improvement of symptoms. The most common adverse events in the ruxolitinib arm were anemia (31%) and thrombocytopenia (34.2%).

In the COMFORT-II, a randomized phase 3 trial, ruxolitinib was compared with BAT and it displays similar findings of marked durable reduction in spleen volume and in performance status (11). A recent study update demonstrated that 53.4% of patients in the ruxolitinib arm achieved a spleen reduction lasting for 3.2 years and 48% of patients

improved or stabilized bone marrow fibrosis. Although the longer exposure, there was no increase of the side effects in comparison with previous studies. The risk of death was reduced by 33% in the ruxolitinib arm (12-14).

Allogeneic stem cell transplant

Allogeneic stem cell transplantation (allo-SCT) is the only potentially curative option for MF patients and is typically reserved for fit patients, whose life expectancy is shorter than 3 years, including DIPPS intermediate-2 and high-risk individuals and patients with unfavorable cytogenetic abnormalities.

Since the initial report of successful allo-SCT in MF (15), several publications have confirmed the curative potential of transplantation, and the adoption of reduced intensity conditioning (RIC) regimens has made allo-SCT applicable to a larger proportion of patients (16). However, there are no randomized controlled trials comparing allo-SCT with any drug therapy or supportive care; nor are there any randomized controlled trials comparing myeloablative conditioning (MAC) with RIC allo-SCT.

In the choice of allo-SCT for MF, we should take into account either the prognosis of disease or the incidence of morbidity and mortality related to the transplant procedure.

Allogeneic transplant: patient selection

The choice of allo-SCT can be based on the prognostic score of the patients which predicts the outcome of the disease at diagnosis and at any time of MF evolution. Population based non controlled studies had demonstrated that median OS after allo-SCT was superior to that after non transplant management in patients with DIPPS intermediate-2 and high-risk score (17-21).

Taking into account either prognostic scoring systems and the more recent molecular risk classification, the following categories should be considered potential candidates for allo-SCT:

1. All patients with intermediate-2 or high-risk disease according to IPSS, DIPPS or DIPSS Plus, and age <70 years;
2. All patients with intermediate-1 risk disease, age <65 years with either refractory, transfusion-dependent anemia or a percentage of blasts in peripheral blood major than 2%, or adverse cytogenetics.

Patients with low–risk disease should not undergo allo-SCT: they should be monitored and evaluated for transplantation if disease progression occurs. Patients with blastic transformation should receive debulking therapy and be reconsidered for transplant after achieving at least a partial remission. Although molecular risk classification for the identification of candidates for allo-SCT among intermediate-1 risk patients deserves further clinical validation, patients in this risk category who are *JAKV617F, CALR* and *MLP* negative or *ASXL1* positive, or both, should be considered for transplant.

Allogeneic transplant: choice of conditioning regimen

Clinical results of standard MAC transplants were reported since 1999 and resulted in non relapse mortality (NRM) rates ranging from 27 to 48% with more favorable results in fit young patients with less advanced disease and better HLA-matching (*Table 2*) (1, 22-28).

TABLE 2 • Myeloablative allogeneic stem cell transplant for Myelofibrosis.

	N. patients	Median age	Conditioning	Graft failure	NRM*	Relapse rate	OS**
Guardiola et al. (22)	55	42 (4-53)	MAC	9%	27%	23%	47%
Daly A. et al. (23)	25	48 (46-50)	MAC	9%	48%	/	41%
Ditschkowski M. et al. (24)	20	45 (22-57)	MAC	n.v.	40%	15%	38%
Kerbauy et al. (25)	104	49 (18-70)	91% MAC	10%	34%	10%	51%
Patriarca F. et al. (1)	100	49 (21-68)	49% MAC	10%	43%	41%	42%
Stewart W.A. et al. (26)	51	49 (19-64)	52% MAC	0	41%	15%	44%
Balle K.K. et al. (27)	289	47 (18-73)	86% MAC	18%	36%	32%	36%

*NMR = non relapse mortality; **OS = overall survival.

In the CIMTR retrospective analysis (10) ideal candidates for MAC were patients younger than 40 years, with no comorbidities and an HLA-identical sibling.

In the last decade, several retrospective and prospective studies have demonstrated feasibility of RIC regimens with NRM rates ranging from 9 to 54% and OS ranging from 34 to 78% (*Table 3*) (6, 21, 29-36). A spectrum of RIC regimens and protocols has shown acceptable NRM and OS. Two prospective studies have been published: Kroeger et al. (29) reported in 104 patients treated with a fludarabine-busulfan conditioning an encouraging 5-year OS of 67%, with 2 year-NRM of 16%. A subsequent study reported by Rondelli et al. (21) with a fludarabin-melphalan preparative regimen observed a significantly poorer outcome after unrelated donor transplants in comparison with HLA-identical sibling transplants, due to toxicity and graft failure. Now days, there is no direct evidence to

TABLE 3 • Reduced Intensity stem cell transplant for Myelofibrosis.

	N. patients	Median age	NRM*	Relapse rate	OS**
Rondelli D. et al. (32)	21	54 (27-68)	9%	9%	78%
Merup M. et al. (33)	10	40 (5-63)	29%	NE	70%
Bacigalupo A. et al. (35)	46	55 (32-68)	24%	19%	45%
Nagi W. et al. (36)	11	51(46-62)	54%	0	46%
Samuelson S. et al. (37)	30	65 (60-78)	30%	30%	45%
Gupta V. et al. (6)	233	55(19-79)	24%	48%	56%
Kroger N. et al. (29)	104	55(32-68)	16%	-	67%
Rondelli D. et al. (21)	66	54.5	40.5%	-	53.5%

*NMR = non relapse mortality; **OS = overall survival.

recommend which conditioning regimen should be preferentially adopted, due to the lack of comparative studies. A phase II randomized study comparing 2 fludarabin-based RIC regimens associated with a different alkylating agent (busulfan versus thiotepa) has been conducted by the Gruppo Italiano Trapianto di Midollo Osseo (GITMO) and the clinical results of this trial will clarify this issue. Moreover, the optimal intensity of the conditioning regimen still needs to be defined: for patients with older age or with comorbidities, or both, a lower intensity regimen is more appropriate, while for patients with advanced disease and good performance status a more intensive regimen should be selected.

Allogeneic transplant: management and prevention of relapse

About 10-18% of MF patients transplanted with MAC regimens experienced relapse within 3 years post transplant (23,25,27,28). Relapse rates after RIC ranged from 29 to 43% (20, 21). Disease-specific markers such as karyotypic abnormality, *JAK2V617F*, *CALR* and *MPL* mutations should be monitored to detect minimal residual disease after allo-SCT. Timing of analysis should be paired with chimerism evaluation.

Alchalby et al. (37) evaluated the impact of *JAK2* genotype, *JAK2V617F* allele burden and clearance of mutation after allo-SCT in 139 MF patients. OS was significantly reduced in multivariate analysis in patients harboring *JAK2* wild-type compared with *JAK2* mutated patients. No significantly influence on outcome was noted for the mutated allele burden. Achievement of *JAK2V617F* negativity after allo-SCT was significantly associated with a decreased incidence of relapse.

In patients with evidence of minimal residual disease or with decreasing donor cell chimerism, discontinuation of immune-suppressive drugs and/or escalated donor lymphocyte infusions (DLI) should be considered to avoid clinical relapse.

In patients who relapse after allo-SCT and do not have severe GvHD, reduction of immunosuppressive drugs or DLI are the treatment strategies of choice: JAK inhibitor treatment is recommended, but remains experimental.

Allogeneic transplant: how to include JAK2 inhibitors in the platform of allogeneic transplant

Taking in account their mechanism of action and biological effects, the JAK2 inhibitors have a potential impact on several steps of the MF treatment pathway. This influence could theoretically be favourable or negative. First, if they are administered in the pre-transplant period, they can enhance feasibility of the procedure, improving performance status and reducing splenomegaly. However, patients responsive to JAK2 inhibitors would be more likely to defer or avoid transplant, at least temporarily, and they could be candidate for it after having lost the response and in presence of more advanced disease.

Second, the inclusion of the JAK2 inhibitors into the conditioning regimen could lower the inflammatory cytokines and reduce GvHD risk, but at the same time, could alter the engraftment dynamic. Third, consolidation or maintenance with JAK2 inhibitors after allo-SCT could eradicate minimal residual disease; however, an impact

on lymphoid reconstitution can be hypothesized.

Since 2010, a few prospective trials incorporating JAK-2 inhibitors in the platform of allogeneic transplant have been initiate (Clinical Trials. Gov NCT01790295; Clinical Trial. gov: NCT01795677), but conclusive results have not been reported yet; moreover, some retrospective studies were already published (38-40).

All these data concern exclusively ruxolitinib administered in the pre-transplant period.

The first information came from the abstract presented at the American Society Haematology Meeting in December 2013 by the French group, which reported 10 severe adverse events occurring within 21 days after ruxolitinib discontinuation (39).

These events, including tumour lysis syndromes or cardiogenic shocks, which occurred during conditioning regimen or in the early period after stem cell reinfusion, had some clinical features in common with the withdrawal syndrome already reported after abrupt suspension of ruxolitinib outside the transplant setting (41) and attributed to a rapid rebound of inflammatory cytokines.

These adverse effects can be prevented by slowly tapering rather than abruptly discontinuing ruxolitinib. In fact, a few retrospective studies (39, 40, 42) in which ruxolitinib was tapered and suspended the day(s) before conditioning did not reported any severe toxicity. Moreover, these trials reported that ruxolitinib reduced splenomegaly or control symptoms in the majority of the patients treated before transplant, with occasional severe haematological adverse effects. All patients engrafted after transplant and incidence of acute GvHD and NRM were in the ranges expected after allo-SCT for MF patients.

The largest retrospective study (43) included 100 pts treated with ruxolitinib before allo-SCT among different Canadian and American Centers. Outcome of ruxolitinib treatment before allo-SCT could be differentiated in 5 conditions: clinical improvement (23 patients), stable disease (31 pts), cytopenia or intolerance (18 pts), progressive splenomegaly (18 pts), leukemic transformation: (13 pts). Patients who obtained clinical improvement with ruxolitinib before transplant had a significative reduction of NRM and relapse incidence and a significative prolongation of OS after transplant. Moreover, response to JAK2 inhibitors, DIPSS and donor type emerged as independent predictors for OS.

Adverse events related to withdrawal syndrome were significantly more common in patients who started tapering or stopped more that 6 days before conditioning. The consensus of European Bone Marrow Transplantation (EBMT)/European Network Leukaemia (ENL) (44) has proposed some guidelines regarding inclusion of ruxolitinib in transplant platform. The experts stated that pre-transplant JAK inhibitor therapy is indicated in patients with symptomatic spleen and/or constitutional symptoms.

The drug should be initiated at least 2 months before transplant and should be titrated to the maximum tolerated dose. Weaning starting to 5-7 days prior to conditioning should be implemented in the attempt to avoid a rebound phenomenon, with the drug stopping the day before conditioning.

JAK2 inhibitors alone may reduce the spleen size and persistent constitutional symptoms, but there is no evidence that suggests modulation of donor cell chimerism or clearance of minimal residual disease: therefore no guideline regarding ruxolitinib administration after transplant can be proposed.

CONCLUSIVE CONSIDERATIONS

In conclusion, the indications of the EBMT/ENL consensus (44) are the following:

- All patients with intermediate-2 or high-risk MF and age <70 years, should be considered candidates for allo-SCT;
- Patients with intermediate-1 disease and age <65 years should be considered for allo-SCT if transfusion dependent anemia, or blasts in peripheral blood >2% or adverse cytogenetics are present;
- Patients with low-risk disease should not be considered for transplant;
- Patients can receive ruxolitinib before transplant to reduce splenomegaly and symptoms and have to stop it the day before conditioning;
- The optimal intensity of the conditioning regimen still needs to be defined;
- A spectrum of reduced intensity conditioning and protocols has shown acceptable NRM and OS;
- Disease–specific markers (in particular *JAK2V67F)* should be monitored to detect minimal residuals disease after allo-SCT.
- Ruxolitinib administration after transplant with the aim of modulating donor cell chimerism or eradicating minimal residual disease warrants further exploration.

REFERENCES

1. Patriarca F, Bacigalupo A, Sperotto A, et al. Allogeneic Hematopoietic Stem Cell Transplantation in Myelofibrosis: the 20-years experience of the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Haematologica. 2008; 93: 1514-22.
2. Geyer HL, Mesa RA. Therapy for myeloproliferative neoplasms: when, which agent and how? Blood. 2014; 124: 3529-37.
3. Tefferi A. Primary myelofibrosis: 2014 update on diagnosis, risk stratification and management. Am J Hematol. 2014; 89: 916-23.
4. Cervantes F. How I treat myelofibrosis. Blood. 2014; 124: 2635-42.
5. Mesa RA, Li CY, Ketterling RP, et al. Leukemic transformation in myelofibrosis with myeloid metaplasia: a single-institution experience with 91 case. Blood. 2005; 105: 973-7.
6. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood. 2009; 113: 2895-901.
7. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood. 2010; 115: 1703-8.
8. Gangat N, Caramazza D, Vaidya R, et al. DIPSS Plus: A refined dynamic international prognostic scoring system for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol. 2011; 29: 392-7.
9. Tefferi A, Lasho TL, Tischer A, et al. The prognostic advantage of calreticulin mutations in myelofibrosis might be confined to type 1 or type 1-like CALR variants. Blood. 2014; 124: 2465-6.
10. Rumi E, Pietra D, Pascutto C, et al. Clinical effect of driver mutations of JAK2, CALR, or MPL in primary myelofibrosis. Blood. 2014; 124: 1062-9.

11. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of Ruxolitinib for myelofibrosis. N Engl J Med. 2012; 366: 799-807.
12. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with Ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012; 366: 787-98.
13. Vannucchi AM, Kantarjian HM, Kiladjian JJ, et al. A pooled analysis of overall survival in COMFORT-I and on COMFORT-II, 2 randomized phase III trials of Ruxolitinib for the treatment of myelofibrosis. Haematologica. 2015; 100: 1139-45.
14. Harrison CL, Vannucchi AM, Kiladjian JJ, et al. Long-term efficacy and safety in COMFORT-II, a Phase 3 Study comparing ruxolitinib with best available therapy for the treatment of myelofibrosis: 5-year final study results. Blood 2015; 126: 59 (Abstract ASH).
15. Dokal I, Jones L, Deenmamode M, et al. Allogeneic bone marrow transplantation for primary myelofibrosis. Br J Haematol. 1989; 71: 158-60.
16. Gupta V, Hari P, Hoffman. Allogeneic hematopoietic cell transplantation for myelofibrosis in the era of Jak2 inhibitors. Blood. 2012; 120: 1367-79.
17. Ditschkowski M, Elmaagacli AH, Trenschel R, et al. Dynamic International Prognostic Scoring System scores, pre - transplant therapy and chronic graft-versus-host disease determine outcome after allogeneic hematopoietic stem cell transplantation for myelofibrosis. Haematologica. 2012 ;97: 1574-81.
18. Scott BL, Gooley TA, Sorror ML, et al. The Dynamic International Prognostic Scoring System for myelofibrosis predicts outcomes after hematopoietic cell transplantation. Blood. 2012; 119: 2657-64.
19. Alchalby H, Yunus DR, Zabelina T, et al. Risk models predicting survival after reduced – intensity transplantation for myelofibrosis. Br J Haematol. 2012; 157: 75-85.
20. Gupta V, Malone AK, Hari PN, et al. Reduced–intensity hematopoietic cell transplantation for patients with primary myelofibrosis: a color analysis form the center for International blood and marrow transplant research. Biol Blood Marrow Transplant. 2014; 20: 89-97.
21. Rondelli D, Goldberg JD, Isola L et al. MPD-RC 101 prospective study of reduced–intensity allogeneic hematopoietic stem cell transplantation in patients with myelofibrosis. Blood. 2014; 124: 1183-91.
22. Guardiola P, Anderson JE, Bandini G, et al. Allogeneic stem cell transplantation for agnogenic myeloid metaplasia: a European Group for Blood and Marrow Transplantation, Société Francaise de Greffe de Moelle, Gruppo Italiano per il Trapianto di Midollo Osseo, and Fred Hutchinson Cancer Research Center Collaborative Study. Blood. 1999; 93: 2831-8.
23. Daly A, Song K, Nevill T, et al. Stem cell transplantation for myelofibrosis: a report from two Canadian Centers. Bone Marrow Transplant. 2003; 32: 35-40.
24. Ditschkowski M, Beelen DW, Trenschel R, et al. Outcome of allogeneic stem cell transplantation in patients with myelofibrosis. Bone Marrow Transplant. 2004; 34: 807-13;
25. Kerbauy DMB, Gooley TA, Sale GE, et al. Hematopoietic cell transplantation as curative therapy for idiopathic myelofibrosis, advanced polycythemia vera, and essential thrombocythemia. Biol Blood Marrow Transplant. 2007; 13: 355-65;
26. Stewart WA, Pearce R, Kirkland KE, et al. The role of allogeneic SCT in primary myelofibrosis: a British Society for Blood and Marrow Transplantation study. Bone Marrow Transplant. 2010; 45: 1587-93.
27. Balle KK, Shrestha S, Sobocinski KA, et al. Outcome of transplantation for myelofibrosis. Biol Blood Marrow Transplant. 2010; 16: 358-67.
28. Robin M, Tabrizi R, Mohty M, et al. Allogeneic haematopoietic stem cell transplantation for myelofibrosis: a report of the Societè Francaise de Greffe de Moelle et de Therapie Cellulaire (SFGM-TC). Br J Haematol. 2011; 152: 331-39.
29. Kroger N, Holler E, Kobbe G, et al. Allogeneic stem cell transplantation after reduced - intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia

Working Party of the European Group for Blood and Marrow Transplantation. Blood. 2009; 114: 5264-70.
30. Shanavas M, Messner HA, Atenafu EG, et al. Allogeneic hematopoietic cell transplantation for myelofibrosis using fludarabine, intravenous busulfan and low dose TBI-based conditioning. Bone Marrow Transplant. 2014; 49: 1162-9.
31. Ciurea SO, Sadegi B, Wilbur A, et al. Effects of extensive splenomegaly in patients with myelofibrosis undergoning a reduced intensity allogeneic stem cell transplantation. Br J Hematol. 2008; 141: 80-3.
32. Rondelli D, Barosi G, Bacigalupo A, et al. Allogeneic hematopoietic stem-cell transplantation with reduced–intensity conditioning in intermediate- or high-risk patients with myelofibrosis with myeloid metaplasia. Blood. 2005 ;105: 4115-9.
33. Merup M, Lazarevic V, Nahi H, et al. Different outcome of allogeneic transplantation in myelofibrosis using conventional or reduced - intensity conditioning regimens. Br J Heamatol. 2006; 135: 367-73.
34. Bacigalupo A, Soraru M, Dominietto A, et al. Allogeneic hemopoietic SCT for patients with primary myelofibrosis: a predictive transplant score based on transfusion requirement, spleen size and donor type. Bone Marrow Transplant. 2010; 45: 458-63.
35. Nagi W, Lim ZY, Krishnamurthy P, et al. Alemtuzumab based reduced intensity conditioning allogeneic haematopoietic stem cell transplantation for myelofibrosis. Leuk Res. 2011; 35: 998-1000.
36. Samuelson S, Sandmaier BM, Heslop HE, et al. Allogeneic haematopoietic cell transplantation for myelofibrosis in 30 patients 60-78 years of age. Br J Haematol. 2011; 153: 76-82.
37. Alchalby H, Badbaran A, Zabelina T, et al. Impact of JAK2V617F mutation status, allele burden, and clearance after allogeneic stem cell transplantation for myelofibrosis. Blood. 2010; 116: 3572-81.
38. Lebon D, Rubio MT, Legrand F, et al. Ruxolitinib For Patients With Primary Or Secondary Myelofibrosis before Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT): A Retrospective Study Of The Société Française De Greffe De Moelle Et De Thérapie Cellulaire (SFGM-TC). Blood. 2013; 122: 2111 (ASH Abstract).
39. Stübig T, Alchalby H, Ditschkowski M, et al. JAK inhibition with ruxolitinib as pretreatment for allogeneic stem cell transplantation in primary or post-ET/PV myelofibrosis. Leukemia. 28: 1736-8.
40. Jaekel N, Behre G, Behning A, et al. Allogeneic hematopoietic cell transplantation for myelofibrosis in patients pretreated with the JAK1 and JAK2 inhibitor ruxolitinib Bone Marrow Transplant. 2014; 49: 179-84.
41. Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. Mayo Clin Proc. 2011; 86: 1188-91.
42. Kröger N, Alchalby H, Ditschkowsky M, et al. Ruxolitinib as pretreatment before allogeneic stem cell transplantation for myelofibrosis. Blood. 2013; 122: 392 (Abstract ASH).
43. Shanavas M, Popat U, Michaelis LC, et al. Outcomes of allogeneic hematopoietic cell transplantation in patients with myelofibrosis with prior exposure to Janus Kinase 1/2 Inhibitors. Biol Blood Marrow Transplant. 2016; 22: 432-40.
44. Kröger NM, Deeg JH, Olavarria E, et al. Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus process by an EBMT/ELN international working group Leukemia. 2015; 29: 2126-33.