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Allogeneic–Adult

Ruxolitinib Therapy Followed by Reduced-Intensity Conditioning for Hematopoietic Cell Transplantation for Myelofibrosis: Myeloproliferative Disorders Research Consortium 114 Study

Vikas Gupta[1,*], Heidi E. Kosiorek[2], Adam Mead[3], Rebecca B. Klisovic[4], John P. Galvin[5], Dmitriy Berenzon[6], Abdulraheem Yacoub[7], Auro Viswabandya[1], Ruben A. Mesa[2], Judith Goldberg[8], Leah Price[8], Mohamed E. Salama[9], Rona Singer Weinberg[10], Raajit Rampal[11], Noushin Farnoud[11], Amylou C. Dueck[2], John O. Mascarenhas[12], Ronald Hoffman[12]

[1] *MPN Program, Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada*
[2] *Mayo Clinic Cancer Center, Phoenix, Arizona*
[3] *MRC Molecular Hematology Unit, MRC Weatherall Institute of Molecular Medicine, BRC Biomedical Research Centre, University of Oxford, Oxford, United Kingdom*
[4] *Division of Hematology, Department of Internal Medicine, The Ohio State University, Columbus, Ohio*
[5] *Feinberg School of Medicine, Northwestern University, Chicago, Illinois*
[6] *Comprehensive Cancer Center, Wake Forest School of Medicine, Winston Salem, North Carolina*
[7] *University of Kansas Medical Hospital, Westwood, Kansas*
[8] *New York University School of Medicine, New York, New York*
[9] *Department of Pathology, University of Utah, Salt Lake City, Utah*
[10] *New York Blood Center, New York, New York*
[11] *Memorial Sloan-Kettering Cancer Center, New York, New York*
[12] *Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York*

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A B S T R A C T

We evaluated the feasibility of ruxolitinib therapy followed by a reduced-intensity conditioning (RIC) regimen for patients with myelofibrosis (MF) undergoing transplantation in a 2-stage Simon phase II trial. The aims were to decrease the incidence of graft failure (GF) and nonrelapse mortality (NRM) compared with data from the previous Myeloproliferative Disorders Research Consortium 101 Study. The plan was to enroll 11 patients each in related donor (RD) and unrelated donor (URD) arms, with trial termination if ≥3 failures (GF or death by day +100 post-transplant) occurred in the RD arm or ≥6 failures occurred in the URD. A total of 21 patients were enrolled, including 7 in the RD arm and 14 in the URD arm. The RD arm did not meet the predetermined criteria for proceeding to stage II. Although the URD arm met the criteria for stage II, the study was terminated owing to poor accrual and a significant number of failures. In all 19 transplant recipients, ruxolitinib was tapered successfully without significant side effects, and 9 patients (47%) had a significant decrease in symptom burden. The cumulative incidences of GF, NRM, acute graft-versus-host disease (GVHD), and chronic GVHD at 24 months were 16%, 28%, 64%, and 76%, respectively. On an intention-to-treat basis, the 2-year overall survival was 61% for the RD arm and 70% for the URD arm. Ruxolitinib can be integrated as pretransplantation treatment for patients with MF, and a tapering strategy before transplantation is safe, allowing patients to commence conditioning therapy with a reduced symptom burden. However, GF and NRM remain significant.

INTRODUCTION

Myelofibrosis (MF) is a chronic hematologic malignancy characterized by variable degrees of anemia and thrombocytopenia, marrow fibrosis, extramedullary hematopoiesis, splenomegaly, cytokine-driven inflammatory symptoms, and an increased risk of transformation to acute myelogenous leukemia (AML) and reduced life expectancy. Dysregulation of the JAK-STAT pathway is a hallmark of MF irrespective of phenotypic driver mutations in *JAK2*, *CALR*, and *MPL* genes. The use of JAK 1/2 inhibitors (JAKis) in patients with MF have led to the control of disease-related symptoms, resulting in approval of ruxolitinib [1,2]. The beneficial effects of ruxolitinib and other JAKis have been limited by their inability to deplete the malignant stem cell clones, however [3].

The trial is registered at www.ClinicalTrials.gov (NCT01790295).

* Correspondence and reprint requests: Vikas Gupta, MD, MPN Program, Princess Margaret Cancer Centre, 610 University Avenue, Toronto, ON, Canada M5G 2M9.
E-mail address: vikas.gupta@uhn.ca (V. Gupta).

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The effectiveness of JAKi therapy is variable, and patients with anemia requiring transfusion, high Dynamic International Prognostic Scoring System (DIPSS) score, or *ASXL1/EZH2* mutations have a significantly shorter duration of response [4,5]. At present, allogeneic hematopoietic cell transplantation (HCT) is the sole available curative treatment for MF, but it is associated with a high incidence of nonrelapse mortality (NRM) due to graft failure (GF), hepatic toxicity, and graft-versus-host disease (GVHD) [6-8].

The use of reduced-intensity conditioning (RIC) has helped decrease the frequency of conditioning-related regimen-related toxicities [9]. The prospective Myeloproliferative Disorders Research Consortium (MPD-RC) 101 Study using a fludarabine and melphalan-based RIC regimen was associated with a high rate of GF (26%) in patients receiving unrelated donor (URD) grafts [10]. Another prospective study from the European Bone Marrow Transplant group using a fludarabine and busulfan-based RIC regimen reported a lower rate of GF (2%); however, 11% of the patients required a stem cell boost, indicating significant graft dysfunction [11].

It was hypothesized that treatment with the JAKi ruxolitinib before HCT might improve the patients' clinical status by decreasing the symptom burden related to splenomegaly and inflammation-related symptoms, thereby improving patient performance status before HCT. Furthermore, it was anticipated that a reduction in splenomegaly with ruxolitinib therapy might improve the rate and degree of hematologic recovery. Moreover, anti-JAK1-mediated down-regulation of cytokine levels might reduce the risk of severe GVHD. The primary concerns regarding this strategy were potential "withdrawal effects" after stopping ruxolitinib before HCT, adverse impacts on engraftment due to drug-induced cytopenias, increased risk of infections due to impaired function of dendritic and natural killer cells, and a potentially decreased graft-versus-leukemia effect [3].

To address these issues, the MPD-RC designed this multicenter trial to explore the potential of combining ruxolitinib with an RIC regimen in patients with MF (MPD-RC Protocol 114). The primary objective of the present study was to evaluate the feasibility of combining ruxolitinib with a fludarabine and busulfan-based RIC regimen likely to increase the likelihood of success after HCT. Success was defined as the patient alive and GF-free on day +100 post-HCT. Key secondary endpoints included hematologic recovery, GF, NRM, acute GVHD (aGVHD), chronic GVHD (cGVHD), relapse, overall survival (OS) and progression-free survival (PFS), and patient-reported outcomes.

METHODS

This investigator-initiated multicenter trial (Figure 1) was coordinated by the MPD-RC and based at the Icahn School of Medicine at Mount Sinai, New York, NY. The trial was conducted at the MPD-RC-approved centers in the United States, Canada, and Europe. The Research and Ethics Boards of each participating institution approved the trial, and all participants provided informed consent. The study protocol is available in the Supplementary Data.

Eligibility Criteria

The eligibility criteria included a documented diagnosis of primary MF (PMF), post-essential thrombocythemia (ET) MF, or post-polycythemia vera (PV) MF in patients age 18 to 70 years with intermediate-2/high-risk disease as assessed by the Dynamic International Prognostic Scoring System (DIPSS) criteria or intermediate-1 with at least 1 of the following additional factors: red cell transfusion dependence, unfavorable karyotype or thrombocytopenia, <20% (later amended to <10%) blasts in the peripheral blood (PB) or bone marrow (BM), and platelet count $\geq 50 \times 10^9$/L. Patients who had received ruxolitinib ≤6 months before study entry were included, provided that they received a stable dose and there was no evidence of loss of response. Patients with clinical or laboratory evidence of cirrhosis or active hepatitis A, B, or C infection, and those requiring therapy with a strong CYP3A4 inhibitor before enrollment were excluded. Eligible donors were matched RDs (6/6 or 5/6 antigen or allele matched) or URDs (10/10 or 9/10 antigen or allele matched).

Pre-HCT Ruxolitinib and Tapering of Ruxolitinib

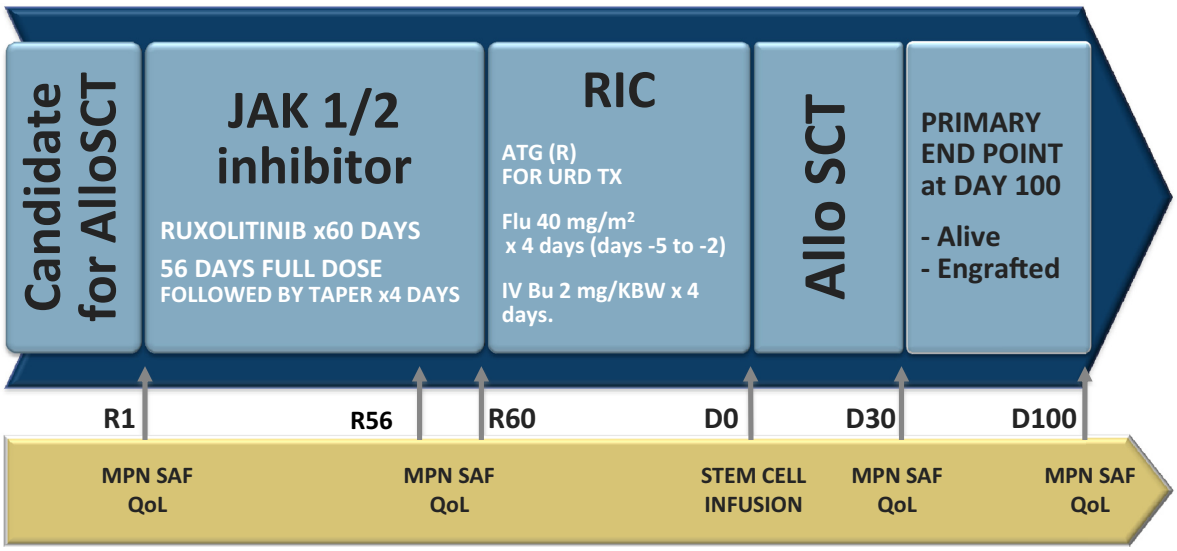
Ruxolitinib was supplied as an investigational product by Incyte (Wilmington, Delaware) for the US centers and by Novartis (Basel, Switzerland) for the centers outside the United States. The goal of pre-HCT treatment was to administer ruxolitinib at full tolerable doses for a minimum of 56 days, followed by tapering over 4 days and then cessation of therapy 1 to 2 days before initiation of the conditioning regimen. The starting dose of ruxolitinib was based on the baseline platelet count. Patients with a platelet count $>200 \times 10^9$/L were started on 20 mg twice daily, those with a platelet count of 100 to 200×10^9/L were started on 15 mg twice daily, and those with a platelet count of 50 to 99×10^9/L were started on 10 mg twice daily. Platelet counts were monitored once weekly, and twice weekly in patients with a platelet count $<50 \times 10^9$/L. Dose adjustments and tapering before HCT were performed according to the study protocol KJL (Supplementary Data 1 and Appendix Table A1). All patients were carefully monitored for withdrawal or cytokine release symptoms before the start of conditioning therapy.

Conditioning Therapy and GVHD Prophylaxis

Conditioning therapy included i.v. fludarabine (40 mg/m^2 daily for 4 days) and i.v. busulfan (2.0 mg/kg daily for 4 days) from days -5 to -2. GVHD prophylaxis was with calcineurin inhibitor, either cyclosporine or tacrolimus, along with methotrexate 10 mg/m^2 on day +1 and 5 mg/m^2 on days +3 and +6. The doses of cyclosporine and tacrolimus were adjusted according to trough blood levels and maintained at 200 to 400 μg/L and 8 to 12 ng/mL, respectively. The calcineurin inhibitor was administered for 6 months, and the dose was tapered in the absence of GVHD. Patients with a URD or mismatched donor received additional GVHD prophylaxis with low-dose antithymocyte globulin (ATG) at doses of 0.5 mg/kg on day -3 and 2.0 mg/kg on days - 2 and - 1. The recommended graft source was mobilized PB.

Study Design

A 2-stage Simon phase II design was used for each of 2 groups of patients, one group receiving grafts from related donors (RDs) and the second receiving grafts from URDs. The goal was to decrease the high rate of GF and NRM reported in the previous MPD-RC 101 study [10]. In the first stage of the trial, the plan was to enroll 11 patients in each of the RD and URD arms and evaluate for failure (defined as death or GF at day 100). As per protocol design, in the URD group, the 2-stage minimax design was used to rule out that the failure rate is ≥50% compared with the alternative that the failure rate is ≤25% with alpha of 0.05 and power of 80%, and in the RD group, the 2-stage design was used to rule out that the failure rate is ≤25% versus the alternative that it is ≤10% in the URD group with the same alpha and power constraints. With these



Abbreviations: ATG, antithymocyte globulin; JAK, Janus kinase; MPD-RC, Myeloproliferative Disorders Research Consortium; RIC, reduced intensity conditioning; SCT, stem cell transplantation; URD, unrelated donor; MPN-SAF, myeloproliferative neoplasm symptom assessment form; QoL, quality of life; R1, first day of ruxolitinib treatment; R56, start of taper of ruxolitinib; R60, last day of ruxolitinib treatment

Figure 1. Study schema.

designs, the plan was not to pursue a second stage if the failure were ≥6 of 11 patients in URD arm and ≥3 of 11 patients in the RD arm. Patients who did not reach the transplant stage due to toxicities related to ruxolitinib, progression of disease or who required splenectomy before HCT were counted as failures. If the trial was to proceed to a second stage, the goal was to accrue a total of 50 patients in the RD arm and 26 patients in the URD arm. A Data Safety and Monitoring Board independent of the study investigators regularly monitored the progress of the trial.

Definitions

DIPSS scores and transfusion dependency were defined in accordance with previously published criteria [12,13]. Neutrophil recovery was defined as first of 3 consecutive days with a neutrophil count $\geq 0.5 \times 10^9$ /L and a platelet count $\geq 20 \times 10^9$ /L without granulocyte colony-stimulating factor or platelet transfusions and maintained for at least 30 days. GF was defined as the failure to achieve adequate neutrophil and platelet counts (primary) or a decline in counts after achievement of sustained adequate counts (secondary) in the absence of a reversible cause of a drop in counts. Regimen-related toxicities were defined according to Bearman's criteria [14]. aGVHD and cGVHD were defined according to previously published criteria [15,16].

MF-associated symptoms, general quality of life (QoL), treatment-relevant QoL, and related symptoms were measured at baseline, before the start of conditioning therapy (day -9), at the start of conditioning (day -5), and during post-BMT follow-up (days +30 and +100 and months +6 and +12). The following questionnaires were used for patient-reported outcomes: the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) [17], Brief Fatigue Inventory (BFI) [18], Functional Assessment of Cancer Therapy–Bone Marrow Transplant [19], and Patient Global Impression of Change [20]. The splenic response to ruxolitinib was measured as the percent reduction in palpable spleen length at the start of conditioning therapy compared with baseline.

Statistical Methods

Baseline patient characteristics and disease-and treatment-related variables were summarized for the RD and URD arms using descriptive summary statistics. Maximum grade toxicities were summarized for each patient according to the time of occurrence. The incidences of hematologic recovery, GF, aGVHD, cGVHD, and NRM were estimated using cumulative incidence methods with death as the competing risk. An intention-to-treat approach was used to determine OS from study entry until death from any cause and included both transplant recipients and patients who did not undergo transplantation. Patients were censored at the last known date alive, if death was not documented. PFS was defined as the interval from study entry until documented disease progression/relapse or death from any cause. OS and PFS were estimated using the Kaplan-Meier method. For symptom assessments and QoL measures, mean changes (with 95% CIs) from baseline were compared using the *t* tests and summarized over time graphically. SAS version 9.4 (SAS Institute, Cary, NC) was used for the analysis.

RESULTS

Baseline patient-, disease-, and transplantation-related characteristics of patients enrolled in stage I of the study in the RD and URD arms are summarized in Table 1. The median age of the study participants was 59 years (range, 39 to 70 years). Almost one-half (48%) of the patients had primary MF, and 52% had post-PV or post-ET MF. High-molecular-risk (HMR) mutations, defined as the presence of *ASXL1, SRSF2, EZH2*, or *IDH1/2* genes, were observed in 10 patients (50%) (Table 1). The majority of patients (81%) were ruxolitinib-naive at the time of study entry. All patients received a PB graft. The median duration of follow-up for survivors was 24 months (range, 9 to 33 months).

Stage I Enrollment

RD Arm

A total of 7 patients were enrolled in the RD arm, in which recipients received a graft from an RD. Three protocol-specified failures occurred in this arm; thus, this arm was closed in accordance with predetermined criteria. Two of these 3 patients did not undergo HCT as originally planned. The first patient had PB blasts of 10% at enrollment along with a complex karyotype, and rapidly progressed to AML while receiving ruxolitinib. Although this transformation was not considered to be related to ruxolitinib, the event was considered a treatment failure. After this event, the protocol was amended to restrict the recruitment to patients in chronic phase (blasts <10%). Another patient receiving ruxolitinib therapy experienced sudden death from an unknown cause. The third failure in this arm was due to primary GF at day +30 (Table 2).

URD Arm

All 14 patients enrolled in the URD arm underwent HCT as planned. Four failures occurred in this arm, including 2 due to secondary GF and 2 due to death within the first 100 days (Table 2). The URD arm met the protocol-specified criteria for proceeding to stage II of the study; however, owing to the poor accrual rates related to widespread use of prolonged ruxolitinib therapy before referral to HCT by the practice community at that time, we decided to halt the trial.

Table 1
Baseline Characteristics of the Study Patients

Characteristics	All Patients (n = 21)	HCT from RD (n = 7)	HCT from URD (n = 14)
Age at study entry, yr, median (range)	59 (39-70)	59 (39-63)	58 (41-70)
Sex, n (%)			
Male	10 (48)	2 (29)	8 (57)
Female	11 (52)	5 (71)	6 (43)
Race, n (%)			
White	19 (90)	5 (71)	14 (100)
Black/African American	1 (5)	1 (14)	0
Asian	1 (5)	1 (14)	0
Diagnosis, n (%)			
PMF	10 (48)	1 (14)	9 (64)
PPV-MF	3 (14)	1 (14)	2 (14)
PET-MF	8 (38)	5 (71)	3 (21)
ECOG PS at study entry, n (%)			
0	9 (43)	3 (43)	6 (43)
1	12 (57)	4 (57)	8 (57)
Ruxolitinib naïve, n (%)	17 (81)	4 (57)	13 (93)
Hemoglobin at study entry, median (range)	8.8 (7.5-11.3)	8.8 (7.5-10.8)	9.4 (8.1-11.3)
WBC at study entry, median (range)	9.1 (2.2-39.1)	6.3 (2.2-33.4)	10.9 (4.9-39.1)
Platelets at study entry, median (range)	211 (61-1979)	211 (88-1979)	213.5 (62-448)
PB blasts at study entry, median (range)	2.0 (0-10)	0.7 (0-10)	2.0 (0-6)
Constitutional symptoms, n (%)	12 (57)	5 (71)	7 (50)
Transfusion dependence, n (%)	4 (19)	3 (43)	1 (7)
DIPSS at study entry, n (%)			
Intermediate-1	5 (24)	3 (43)	2 (14)
Intermediate-2	12 (57)	4 (57)	8 (57)
High	4 (19)	0	4 (29)
BM fibrosis grade at study entry, n (%)			
Grade 2	5 (28)	2 (33)	3 (25)
Grade 3	13 (72)	4 (67)	9 (75)
Missing	3	1	2
Cytogenetics, n (%)			
Normal	9 (42)	4 (57)	5 (36)
Abnormal standard risk	3 (14)	1 (14)	2 (14)
Abnormal high risk	4 (19)	1 (14)	3 (21)
Unknown/failed	2 (9)/3 (14)	0/1 (14)	2 (14) /2 (14)
MPN phenotype driver mutation (n = 20), n (%)			—
JAK2	11 (55)*	4 (57)*	7 (54)*
MPL	2 (10)*	1 (14)	1 (8)*
CALR	8 (40)*	3 (43)*	5 (38)
Triple negative	1 (5)	1 (14)	—
HMR mutations, n (%)†			
ASXL1	8 (40)	2 (29)	6 (46)
SRSF2	1 (5)	—	1 (8)
IDH1/2	1 (5)	1 (14)	—
EZH2	4 (20)	2 (29)	2 (15)
HMR profile, n (%)‡			
Yes	10 (50)	3 (43)	7 (54)
No	10 (50)	4 (57)	6 (46)
Palpable spleen length at study entry (n = 17), median (range)	11.0 (0-20.2)	11.5 (0-20)	11.0 (0-20)
Underwent HCT, n (%)	19 (91)	5 (71)	14 (100)

ECOG indicates Eastern Cooperative Oncology Group; HMR, high molecular risk.

* Two patients were positive for double driver mutations, one with *JAK2* and *CALR* and the other with *JAK2* and *MPL*.

† HMR, high molecular risk mutations: *ASXL1*, *SRSF2*, *EZH2*, and *IDH1/2*.

‡ HMR profile, presence of at least 1 of the HMR mutations.

Among the 21 enrolled patients, 19 (5 of 7 in the RD arm and all 14 in the URD arm) underwent HCT as planned.

Pre-HCT Ruxolitinib Therapy (n = 21)

As noted above, 2 patients in the RD arm did not proceed to HCT, 1 because of progression to AML pre-HCT and the other due to sudden death of unknown cause. In all 19 patients undergoing HCT, ruxolitinib was tapered successfully with no evidence of cytokine release, withdrawal symptoms, or rebound splenomegaly. There were no delays in planned HCT in any of the patients after ruxolitinib discontinuation. Grade ≥3 anemia was seen in 8 of these 19 patients (42%), and thrombocytopenia occurred in 5 (26%). One patient had a serious adverse event related to *Legionella* pneumonia necessitating hospital admission.

Information on MPN-SAF scores was available for all 19 patients undergoing HCT at study entry and before the start of conditioning. Significant improvements in MPN-SAF score were seen in 9 patients (47%), including 6 patients with a >50% reduction and 3 patients with a 25% to 50% reduction. Four patients had a nonpalpable spleen at baseline. Among the 11 patients undergoing HCT with available spleen data, 4 patients had a >50% reduction in spleen size, 1 patient had a 25% to 50% reduction in spleen size, and 6 patients had no improvement from baseline to the end of ruxolitinib treatment.

Post-HCT Outcomes

Hematologic Recovery and GF

The median time to neutrophil recovery and platelet recovery was 23 days (95% CI: 13 - 31) and 30 days (95% CI : 18 – 57), respectively. Median donor chimerism on unsorted peripheral blood was 97% (range 65% -100%) 90% (range, 44 –100%), and 98% (range 57% – 100%) on days +30, +60, and +100, respectively. Three patients experienced GF; 1 patient with primary GF and 2 patients with secondary graft failure. Both patients with secondary GF had >95% donor engraftment on day +30, and then subsequently developed drop in counts. The cumulative incidence estimate of GF at 24 months was 16% (95% CI: 5% – 46%) (Figure 2A). One patient with primary GF had no improvement in splenomegaly or MPN-SAF score before undergoing HCT (UPN 9; Table 2). Two patients with graft rejection (UPNs 2 and 7; Table 2) had significant improvements in spleen size and MPN-SAF score.

Infectious and Noninfectious Complications in the First 100 Days Post-HCT

Fever during neutropenia/sepsis or pneumonia was observed in 8 of the 19 patients (42%). One patient developed respiratory syncytial virus pneumonia, producing an acute respiratory distress syndrome type of picture and resulting in multiorgan failure and death (UPN 11; Table 2). Two patients had significant bleeding complications, and 1 of these patients developed a spontaneous spinal epidural hematoma (UPN 8; Table 2). Severe hepatic toxicity was seen in 4 patients (21%), which contributed to death in 2 patients (UPNs 7 and 9; Table 2). These toxicities were considered regimen-related. Other regimen-related grade 3 toxicities included electrolyte abnormalities, hyperglycemia, cardiac and renal dysfunction, reported in 26%, 16%, 5%, and 5% of patients, respectively.

aGVHD and cGVHD

A total of 12 patients developed acute GVHD (aGVHD), including 3 with grade I, 6 with grade II, and 3 with grade III aGVHD. The cumulative incidence for grade I/II and grade III aGVHD by 24 months was 48% (95% CI, 29% to 79%) and 16% (95% CI, 5% to 46%), respectively (Figure 2B). No patient had grade IV or steroid-refractory aGVHD.

Of the 16 patients alive on day 100, 11 developed cGVHD. Six of these 11 patients developed cGVHD that progressed from aGVHD, and the other 5 developed de novo cGVHD. The cumulative incidence of cGVHD at 24 months was 76% (95% CI, 50% to 100%) (Figure 2C). The 11 patients with cGVHD included 8 with mild cGVHD and 3 with moderate cGVHD. No cases of severe cGVHD were observed.

NRM, OS, and PFS

Two of the 19 patients undergoing HCT experienced relapse. The cumulative incidence of NRM in patients undergoing HCT was 16% (95% CI, 5% to 46%) at 100 days and 28% (95%, CI 13% to 63%) at 2 years (Figure 2A). On an intention-to-treat

Table 2
Summary of Protocol-Specified Failures from Study Enrollment to Day +100 Post-HCT

UPN	Age, yr	Donor Type	DIPSS	Time of Failure	Primary Cause of Failure	Comment
01	41	Related	Intermediate-1 with complex cytogenetics	45 days after ruxolitinib	Progressed to AML	Baseline PB blasts 10%, increased to 39% on ruxolitinib therapy. Taken off study to pursue treatment with decitabine.
9	61	Related	Intermediate-2	Day 30 after HCT	Primary GF	No response to ruxolitinib for spleen or symptoms pre-HCT; additional post-transplantation complications included hepatic toxicity.
19	59	Related	High	1 day after ruxolitinib	Sudden death	Unknown cause of death
02	62	Unrelated	Intermediate-2	Day 60 after HCT	Secondary GF	9/10 MUD; HCT complicated by hepatic toxicity, GVHD, and infections; counts dropped after initial recovery, and a second HCT was performed.
07	60	Unrelated	Intermediate-1 with thrombocytopenia	Day 100 after HCT	Secondary GF	Hepatic toxicity grade 3; counts dropped after initial recovery.
08	53	Unrelated	High risk	Death at <100 days	Intracranial hemorrhage	Spinal epidural hematoma, grade III acute GVHD, platelet count 36×10^9 /L, and no clotting abnormalities at the time of hematoma
11	70	Unrelated	Intermediate-2	Death at <100 days	Infectious complications	Respiratory syncytial virus pneumonia, acute respiratory distress syndrome, and multiorgan failure

UPN indicates unique patient number.

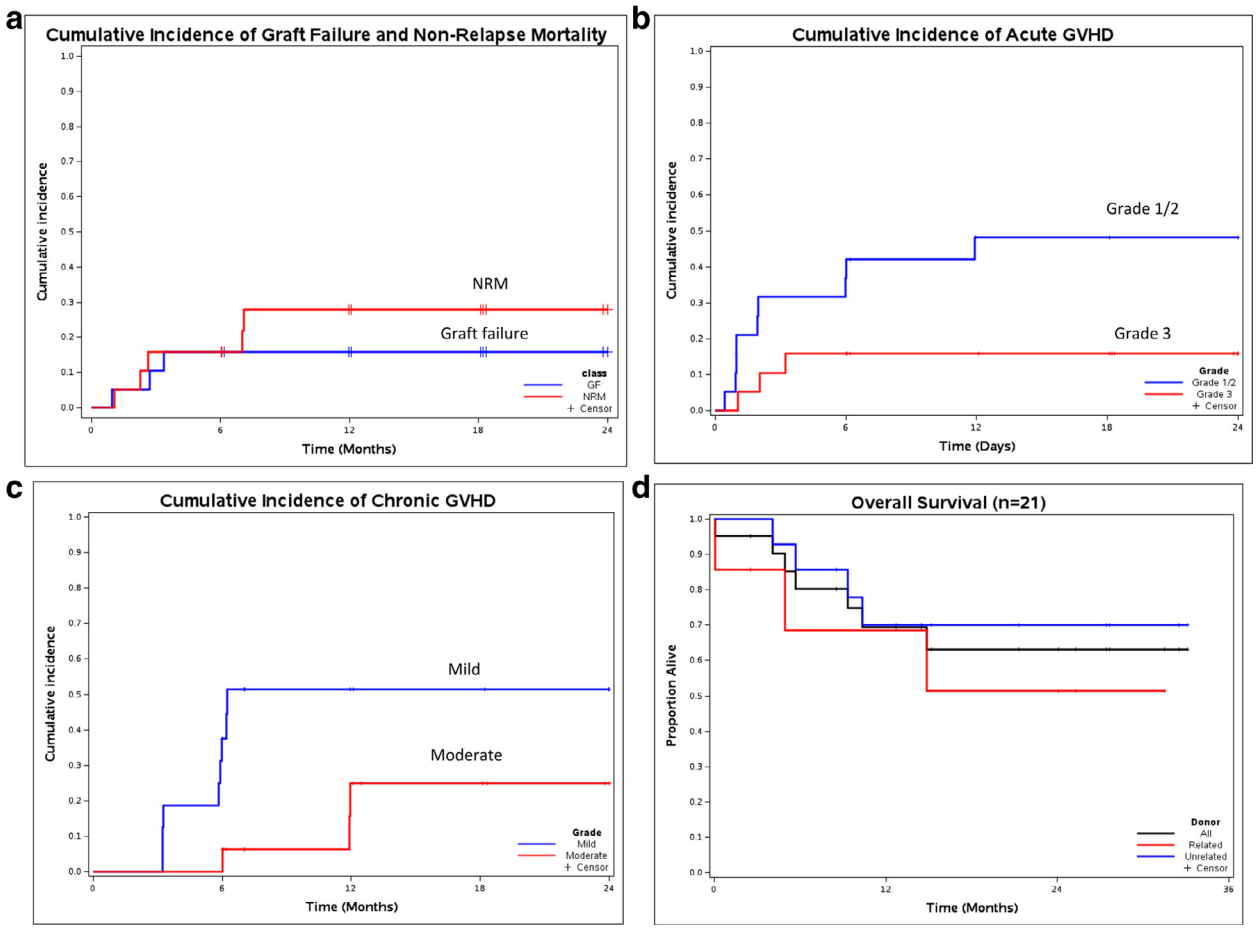


Figure 2. Post-HCT outcomes. (A) Cumulative incidences of GF (16%) and NRM (28%) at 2 years. (B) Cumulative incidences of grade I/II (48%) and grade III (16%) aGVHD. (C) Cumulative incidences of mild (55%) and moderate (21%) cGVHD. (D) OS, on an intent-to-treat basis at 2 years, for all patients (63%), patients undergoing HCT from an RD (51%), and undergoing HCT from a URD (70%).

basis, the 2-year OS was 63% (95% CI, 45% to 90%) for all study participants (n = 21), 51% (95% CI, 24% to 100%) for the RD arm (n = 7), and 70% (95% CI, 49% to 100%) for the URD arm (n = 14) (Figure 2D). The corresponding PFS values at 2 years were 59% (95% CI, 40% to 86%), 51% (95% CI, 24% to 100%), and 63% (95% CI, 42% to 95%), respectively. No difference in survival was seen between patients who had 1 of the HMR mutations and patients without HMR ($P = .99$). For patients who underwent HCT, the 2-year OS was 66% (95% CI, 46% to 93%) for all patients, 60% (95% CI, 29% to 100%) for the RD arm, and 70% (95% CI 49% to 100%) for the URD arm.

Patient-Reported Outcomes

MPN-SAF

Mean changes from baseline are displayed for BFI fatigue and MPN-SAF TSS score at each time point in Figure 3A. Significant changes from baseline were seen for BFI worst fatigue at 30 days (mean, 1.7; 95% CI, 0.25 to 3.08; $P = .03$). No significant changes from baseline were seen for the MPN-SF TSS, because all 95% CIs included 0. There was a trend toward better survival for patients who had a ≥25% improvement in MPN-SAF TSS compared with those with a <25% improvement (77% [95% CI, 53% to 100%] versus 56% [95% CI, 31% to 100%]; $P = .27$).

Functional Assessment of Cancer Therapy–Bone Marrow Transplant

Patients reported significant (worsening) changes from baseline in functional well-being at all post-transplantation time points and in physical well-being at 30 days and 1 year (Figure 3B). Significant changes in the BMT scale were observed at 30 days and 6 months.

Patient Global Impression of Change

At 30 days post-HCT, 11 of 18 patients (61%) reported feeling "worse" ("a little worse," "moderately worse," or "very much worse") for both physical condition and overall QoL compared with baseline (Figure 3C).

DISCUSSION

This is the first prospective study reporting on integration of JAKis before HCT in patients with myelofibrosis using a well-defined approach. Although integrating JAKi therapy with HCT protocols is theoretically attractive, controversial data have emerged in the last few years. Preliminary results from a prospective study (JAK-ALLO) to examine JAKi use in the HCT setting showed serious adverse events in the peritransplantation period, which included cardiogenic shock and tumor lysis syndrome, resulting in a hold on recruitment [21]. It is

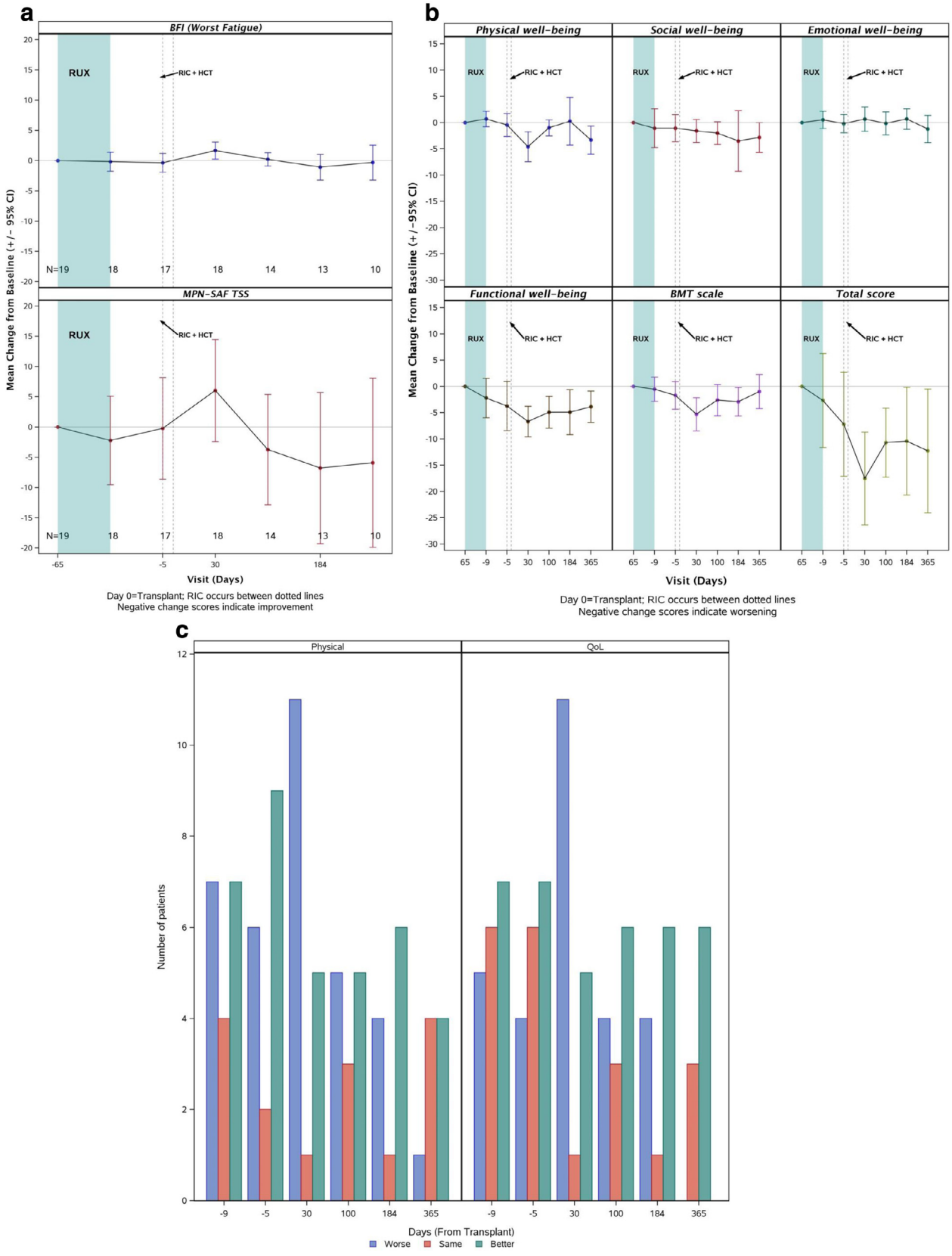


Figure 3. Patient-reported outcomes, changes from baseline. (A) BFI and MPN-SAF. (B) Functional Assessment of Cancer Therapy-Bone Marrow Transplant. (C) Patient Global Impression of Change (PGIC).

speculative that the abrupt discontinuation of JAKis before HCT in the JAK-ALLO study might have contributed to some of these events in that study. In another retrospective study, serious adverse events of rebound splenomegaly necessitating splenectomy and respiratory distress syndrome were reported in 2 patients, delaying HCT. Both these patients stopped JAKi therapy >7 days before conditioning therapy [22].

Retrospective studies have described variable approaches for the use of JAKis before HCT, and most of these studies did not provide details regarding the side effects of JAKi therapy before HCT [23,24]. Moreover, selection bias is an issue, because these studies did not analyze results in an intention-to-treat approach. In this prospective clinical trial, using a tapering strategy with cessation of ruxolitinib treatment the day before the start of conditioning therapy, we did not observe any cytokine release or withdrawal symptoms, rebound splenomegaly, or delay in HCT in any patients. This strategy allowed several patients to undergo HCT with a reduced symptom burden.

Although this strategy is feasible, it is important to note that ruxolitinib might not be suitable for all patients with MF before HCT, given that the first patient enrolled in the study had accelerated-phase disease and progressed rapidly to AML while receiving ruxolitinib. Such patients likely would benefit from cytoreductive strategies. GF remains a major barrier, and JAKi therapy alone might not be able to overcome this barrier. A better understanding of the biology of GF is needed to improve outcomes. The incidence of other post-HCT complications, such as regimen-related toxicities, infectious complications, aGVHD and cGVHD, and NRM, were similar to the reported data for patients undergoing HCT for MF without JAKi therapy [10,11,25]. These findings suggest that the graft-versus-leukemia effect is not compromised with this strategy, which was a concern with the initial design. Of note, cGVHD was mainly mild, and severe cGVHD was not observed in any patients. Preclinical models have demonstrated beneficial effects of JAKi therapy on GVHD when used in the post-transplantation setting [26,27], and several studies are evaluating the role of JAKi therapy in the treatment of steroid-refractory aGVHD and cGVHD. There are no reported data on impact of HCT on MF-related symptom burden and QoL parameters. Using well-validated instruments, our study showed that all patient reported outcomes worsened on day +30 post-HCT, followed by gradual slow improvement. These findings are similar to previous reports in patients with myeloid malignancies [28] and provide useful information for patient counseling.

Our study is limited by its small sample size, because of the premature closure. Therefore, our results must be interpreted with caution. The RD arm did not meet the predetermined criteria for proceeding to stage II, because 2 patients did not reach the transplantation stage due to progression to AML and sudden death on ruxolitinib. Although, URD met the protocol specified criteria for proceeding to stage II, the protocol steering committee carefully reviewed all the stage I data as well recruitment on enrolled patients. Accrual to this study was challenging, because most of the patients referred for HCT were already heavily exposed to ruxolitinib. Even though some patients had a significantly reduced symptom burden before HCT, rates of GF and NRM were not reduced, and were comparable to previously published data. Despite these limitations, however, the observations of this study are clinically useful, allowing for integration of JAKi therapy in the pre-HCT phase in appropriate patients. Tapering of JAKis immediately before administration of the conditioning regimen allows patients to start conditioning with a reduced disease burden. Further understanding of the biology of GF is required to overcome this hurdle in MF patients undergoing HCT.

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Authorship statement: V.G., A.M., J.G., L.P., R.A.M., and R.H. designed the study; V.G., R.B.K., J.P.G., D.B., A.Y., A.V., J.O.M., and R. H. enrolled patients; H.E.K. and A.C.D. performed statistical analysis and provided data management support; V.G., H.E.K., A.M., and R. H. interpreted data; M.E.S., R.S.W., R.R., and N.F. provided laboratory support; V.G. and H.E.K. wrote the manuscript; and all authors reviewed the manuscript and approved it for submission.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.bbmt.2018.09.001.

APPENDICES

Table A1
Schedule for Tapering of Ruxolitinib

Dose before Day -9	Dose on Day -9	Dose on Day -8	Dose on Day -7	Dose on Day -6	Dose on Day -5
20 mg b.i.d.	15 mg b.i.d.	10 mg b.i.d.	5 mg b.i.d.	5 mg o.d.	None
15 mg b.i.d.	10 mg b.i.d.	10 mg b.i.d.	5 mg b.i.d.	5 mg o.d.	None
10 mg b.i.d.	10 mg b.i.d.	10 mg b.i.d.	5 mg b.i.d.	5 mg o.d.	None
5 mg b.i.d.	5 mg b.i.d.	5 mg b.i.d.	5 mg b.i.d.	5 mg o.d.	None

b.i.d. indicates twice daily; o.d., once daily.

REFERENCES

1. 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.
2. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366:787–798.
3. Devlin R, Gupta V. Myelofibrosis: to transplant or not to transplant? *Hematology Am Soc Hematol Educ Program*. 2016;2016:543–551.
4. Patel KP, Newberry KJ, Luthra R, et al. Correlation of mutation profile and response in patients with myelofibrosis treated with ruxolitinib. *Blood*. 2015;126:790–797.
5. Spiegel JY, McNamara C, Kennedy JA, et al. Impact of genomic alterations on outcomes in myelofibrosis patients undergoing JAK1/2 inhibitor therapy. *Blood Adv*. 2017;1:1729–1738.
6. Gupta V, Hari P, Hoffman R. Allogeneic hematopoietic cell transplantation for myelofibrosis in the era of JAK inhibitors. *Blood*. 2012;120:1367–1379.
7. Wong KM, Atenafu EG, Kim D, et al. Incidence and risk factors for early hepatotoxicity and its impact on survival in patients with myelofibrosis undergoing allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2012;18:1589–1599.
8. Slot S, Smits K, van de Donk NW, et al. Effect of conditioning regimens on graft failure in myelofibrosis: a retrospective analysis. *Bone Marrow Transplant*. 2015;50:1424–1431.
9. Gupta V, Kroger N, Aschan J, et al. A retrospective comparison of conventional intensity conditioning and reduced-intensity conditioning for allogeneic hematopoietic cell transplantation in myelofibrosis. *Bone Marrow Transplant*. 2009;44:317–320.
10. 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;124:1183–1191.
11. Kröger 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;114:5264–5270.
12. 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;115:1703–1708.
13. Gale RP, Barosi G, Barbui T, et al. What are RBC-transfusion-dependence and -independence? *Leuk Res*. 2011;35:8–11.
14. Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol*. 1988;6:1562–1568.
15. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Group Report. *Biol Blood Marrow Transplant*. 2005;11:945–956.
16. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825–828.
17. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. *J Clin Oncol*. 2012;30:4098–4103.
18. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer*. 1999;85:1186–1196.
19. Rao D, Butt Z, Rosenbloom S, et al. A comparison of the Renal Cell Carcinoma-Symptom Index (RCC-SI) and the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI). *J Pain Symptom Manage*. 2009;38:291–298.
20. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11:570–579.
21. Robin M, Francois S, Huynh A, et al. Ruxolitinib before allogeneic hematopoietic stem cell transplantation (HSCT) in patients with myelofibrosis: a preliminary descriptive report of the JAK ALLO study, a phase II trial sponsored by Goelams-FIM in collaboration with the Sfgmtc. *Blood*. 2013;122:306.
22. 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;22:432–440.
23. 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*. 2014;28:1736–1738.
24. 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;49:179–184.
25. Gupta V, Malone AK, Hari PN, et al. Reduced-intensity hematopoietic cell transplantation for patients with primary myelofibrosis: a cohort analysis from the Center For International Blood And Marrow Transplant Research. *Biol Blood Marrow Transplant*. 2014;20:89–97.
26. Carniti C, Gimondi S, Vendramin A, et al. Pharmacologic inhibition of JAK1/JAK2 signaling reduces experimental murine acute GVHD while preserving GVT effects. *Clin Cancer Res*. 2015;21:3740–3749.
27. Spoerl S, Mathew NR, Bscheider M, et al. Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease. *Blood*. 2014;123:3832–3842.
28. Gupta V, Panzarella T, Li L, et al. A prospective study comparing the outcomes and health-related quality of life in adult patients with myeloid malignancies undergoing allogeneic transplantation using myeloablative or reduced-intensity conditioning. *Biol Blood Marrow Transplant*. 2012;18:113–124.