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A Prospective Pilot Study of Graft-versus-Host Disease Prophylaxis with Post-Transplantation Cyclophosphamide and Ruxolitinib in Patients with Myelofibrosis

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Keywords
Allogeneic stem cell transplantation · Myelofibrosis · Post-transplant cyclophosphamide · Ruxolitinib

Abstract
Introduction: This prospective study evaluated a calcineurin inhibitor-free graft-versus-host disease (GVHD) prophylaxis regimen of ruxolitinib in combination with post-transplant cyclophosphamide (PTCy). ***Patents and Methods:*** Twenty patients with primary or secondary myelofibrosis were prospectively enrolled. Reduced intensity conditioning was performed, followed by allogeneic stem cell transplantation from related ($n = 7$) or unrelated ($n = 13$) donors. GVHD prophylaxis included only PTCy and ruxolitinib (45 mg) from day–7 to day–2, and 15 mg from day+5 to day+100. This trial was registered at www.clinicaltrials.gov as #NCT02806375. ***Results:*** Primary engraftment was documented in 17 patients. One patient experienced primary graft failure and 2 died before engraftment. Eleven patients demonstrated severe poor graft function (SPGF), which required ruxolitinib dose reduction. The regimen was well tolerated, with grade 3–4 non-haematological toxicity in 30%, viral reactivation in 45%, and severe sepsis in 15% of patients. The incidence of acute GVHD grade II–IV was 25%, grade III-IV GVHD was 15%, and moderate chronic GVHD was 20%, with no severe cases. Only 2 patients required systemic steroids. Haematological relapse was documented in 1 patient. Two-year non-relapse mortality was 15%, 2-year overall survival was 85%, and 2-year event-free survival was 72%. ***Conclusion:*** GVHD prophylaxis with PTCy and ruxolitinib is associated with low toxicity, good acute and chronic GVHD control, and low relapse incidence. However, the relatively high rate of SPGF should be taken into account. SPGF could possibly be mitigated by ruxolitinib dose reduction.

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Introduction

Allogeneic haematopoietic stem cell transplantation (alloHSCT) is the only treatment modality with curative potential in patients with primary and secondary myelofibrosis (MF) [1]. However, alloHSCT in MF patients is associated with relatively high rates of non-relapse mortality (NRM), early relapse, and primary graft failure (PGF) [2] compared to other haematological disorders (for example, acute leukaemias) [3]. The most common causes of death after alloHSCT are MF progression or relapse, acute and chronic graft-versus-host disease (GVHD), infections, and organ toxicity [2].

Several studies report successful outcomes after alloHSCT in combination with pre-transplant Janus kinase (JAK) 1/2 inhibitors. However, this bridge therapy can be associated with withdrawal syndrome, and responses are obtained in only 30–50% of patients [4]. On the other hand, GVHD prophylaxis with post-transplant cyclophosphamide (PTCy) [5] and improved supportive care is a promising approach to significantly reduce NRM [6]. There is growing evidence that PTCy is effective for GVHD prevention not only in haploidentical transplants, but also in matched unrelated transplants [7]. Therefore, a PTCy-based regimen was used in our study.

According to recent recommendations, peripheral blood stem cells (PBSCs) are the most appropriate stem cell source in patients with MF [1]. However, attempts to apply single-agent PTCy prophylaxis to PBSC transplantation were unsuccessful [8]. Thus, PTCy is usually combined with a second agent, such as a calcineurin inhibitor or mycophenolate mofetil [9]. However, additional immunosuppressive agents increase the rate of infectious complications and reduce the graft-versus-leukaemia (GVL) effect.

In our study, we investigated the combination of PTCy and the JAK 1/2 inhibitor ruxolitinib for GVHD prophylaxis. Our hypothesis that ruxolitinib might be effective as part of a GVHD prophylaxis regimen was supported by preclinical studies demonstrating that the JAK-signal transducer and activator of transcription (JAK-STAT) pathway is one of the major lymphocyte activation pathways in GVHD pathogenesis [10], as well as clinical studies in which ruxolitinib was found to be one of the most effective agents for steroid-refractory acute and chronic GVHD [11]. Furthermore, preclinical data suggest that ruxolitinib might prevent GVHD while preserving GVL [12], leading to a reduced relapse rate. Nonetheless, there is no prospective data on the administration of ruxolitinib as GVHD prophylaxis. To evaluate the efficacy of ruxolitinib as a relapse and GVHD prevention agent, we conducted a prospective study in patients with MF.

Materials and Methods

Between 2015 and 2018, 20 patients with primary MF, post-essential thrombocythaemia, and post-polycythaemia vera MF were enrolled in a pilot prospective study (NCT02806375, clinicaltrials.gov) at Pavlov First Saint Petersburg State Medical University. Patient characteristics are summarised in Table 1 and online supplementary Table S3 (for all online suppl. material, see www.karger.com/doi/10.1159/000506758). All patients were treated with pre-transplant ruxolitinib for a median time of 7.4 months (range 2.6–22.3) and continued to receive ruxolitinib (45 mg/day) from day–7 until day–2. Reduced intensity conditioning was performed with fludarabine (180 mg/m^2) and busulfan (10 mg/kg) [13]. GVHD prophylaxis included PTCy (50 mg/kg) on days+3 and +4 and ruxolitinib (15 mg) daily from day+5 to +100. In cases of severe poor graft function (SPGF), ruxolitinib dose was reduced from 15 to 10 mg/day. The study was approved by the Local Ethical Committee of Pavlov First Saint Petersburg State Medical University. All patients signed the informed consent form.

The primary endpoint was the incidence of acute GVHD grade II–IV and chronic moderate and severe GVHD, according to NIH guidelines [14]. The secondary endpoints were overall survival (OS) and event-free survival (EFS), incidence of relapse, PGF, and SPGF. When EFS was calculated, death, relapse, and PGF were defined as events.

The study termination rules included 4 consecutive or 8 overall cases of grade III–IV acute GVHD and 3 consecutive or 6 overall cases of PGF.

Diagnoses were made according to 2016 World Health Organisation criteria. Bone marrow fibrosis grade was assessed according to the European consensus on grading bone marrow fibrosis [15]. Fourteen patients had intermediate-2, 2 had intermediate-1, and 4 had high Dynamic International Prognostic Scoring System Plus (DIPSS Plus) risk [16].

Haematological remission was defined as disappearance of all clinical signs of MF. Bone marrow fibrosis regression was assessed by histological examination at D (day)+60, D+180, and D+365. Molecular monitoring of minimal residual disease was performed using quantitative reverse transcription polymerase chain reaction (qRT-PCR) of *JAK2*, *MPL*, and *CALR* mutated genes.

Toxicity was assessed using Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Sepsis and severe sepsis were diagnosed based on International Guidelines for Management of Severe Sepsis and Septic Shock [17]. Invasive mycosis was diagnosed in cases of probable or proven infection according to EORTC/MSG guidelines [18]. Veno-occlusive disease (VOD) was diagnosed and graded based on modified Seattle criteria [19].

PGF was defined as complete absence of donor chimerism in bone marrow aspirate by day+40. SPGF was defined as levels of neutrophils <500/μL, haemoglobin <70 g/L, or platelets <20,000/μL at least within 2 weeks after D+30 in the presence of full donor chimerism.

Peripheral blood was collected from 20 patients at D-7, D0, D+3, D+7, D+21, D+30, D+60, and D+100. Samples were centrifugated at 1,000 *g* for 15 min at 4 °C. Within 1 h after collection, serum was aliquoted and then stored at –80 °C.

A high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) method was developed for the measurement of ruxolitinib in human plasma in the Research Laboratory of Toxicology and Drug Monitoring at the Nikiforov Russian Center of Emergency and Radiation Medicine, EMERCOM of Russia. The method was based on a publication by Veeraraghavan et al. [20]. Analyses were performed using HPLC Agilent 1200 with triple quadrupole mass spectrometer Agilent 6460 with electrospray ionisation (Agilent Technologies, USA) (online suppl. Methods).

The quantitative detection of interleukin (IL)-8 (IL-8), interferon gamma, IL-17, and IL-1β was performed using commercially available enzyme-linked immunosorbent assay kits (cytokine, RF) according to the manufacturer's instructions. To determine *STAT5B*, *JAK1*, and *JAK2* gene expression levels, qRT-PCR was performed.

All statistical tests were two-sided, and differences with *p* values less than 0.05 were considered significant. The survival distributions for OS and EFS were calculated using Kaplan-Meier methodology with 95% confidence intervals (CI). Cumulative incidence analysis was used for NRM. Statistical comparisons were performed using the Wilcoxon matched pairs test and Mann-Whitney test for continuous variables. All statistical analyses were conducted in SAS 9.3 (SAS Institute Inc.). Additional information is summarised in Supplemental Methods.

Results

The median follow-up was 27 months (range 1–51). Primary engraftment was documented in 17 patients (Table 1). Two patients died before engraftment, and 1 died after engraftment. The median time to neutrophil engraftment was 27 days (18–44), to platelet engraftment was 38 days (15–219), and to achievement of red blood cell transfusion independence was 59 days (20–540). Two patients died before engraftment due to severe *Pseudomonas aeruginosa* sepsis (n = 1) and gastrointestinal bleeding (n = 1). One patient died at day+115 due to thrombotic microangiopathy and infectious complications after cyclosporine A and steroid therapy due to acute GVHD grade 3. One patient experienced PGF. The patient is alive and in remission 1 year after a second alloHSCT.

Fifty-five percent of patients (n = 11) experienced SPGF (Fig. 1b). In 2 patients, SPGF resolved without ruxolitinib dose modifications. Ruxolitinib dose reduction from 15 to 10 mg/day was performed in 8 patients with SPGF. In one of them, SPGF resolved only at day+77, and in another, SPGF resolved after ruxolitinib discontinua-

Table 1. Patient characteristics and results

Age, years	51 (32–64)
Sex	
Male	10 (50)
Female	10 (50)
Diagnosis	
PMF	14 (70)
Post-PV-MF	3 (15)
Post-ET-MF	3 (15)
Risk profile according to DIPSSplus	
Intermediate-1	2 (10)
Intermediate-2	14 (70)
High	4 (20)
Blast crisis	0
Palpable spleen size at transplant	
≥10 cm	6 (30)
<10 cm	7 (35)
Splenectomy	7 (35)
Time between splenectomy and alloHSCT, months	2.60 (0.17–4.50)
Fibrosis grade before alloHSCT	
MF-2	8 (40)
MF-3	12 (60)
Mutational status	
JAK2V617F-positive	13 (65)
CALR-positive	4 (20)
MPL	2 (10)
Triple negative	1 (5)
Karyotype	
Normal	14
t(6;11)(p25;q12)	1
del(13q21)	1
Trisomy 8	3
Unknown	1
Time of ruxolitinib therapy before alloHSCT, months	7.4 (3.0–22.0)
Response at the moment of alloHSCT	
Clinical improvement	7 (35)
Stable disease	12 (60)
Progression	1 (5)
HCT-CI	
0	10 (50)
1	6 (30)
2	3 (15)
3	1 (5)
CD34+ cells/kg × 10^6	6.9 (1.4–12.0)
Donor	
HLA-identical sibling	3 (15)
Haploidentical	4 (20)
Unrelated	
HLA-matched	11 (55)
HLA-mismatched 9/10	2 (10)
Stem cell source	
Bone marrow	1 (5)
Peripheral blood	19 (95)

Data are presented as median (range) or n (%). DIPSSplus, Dynamic International Prognostic Scoring System Plus.

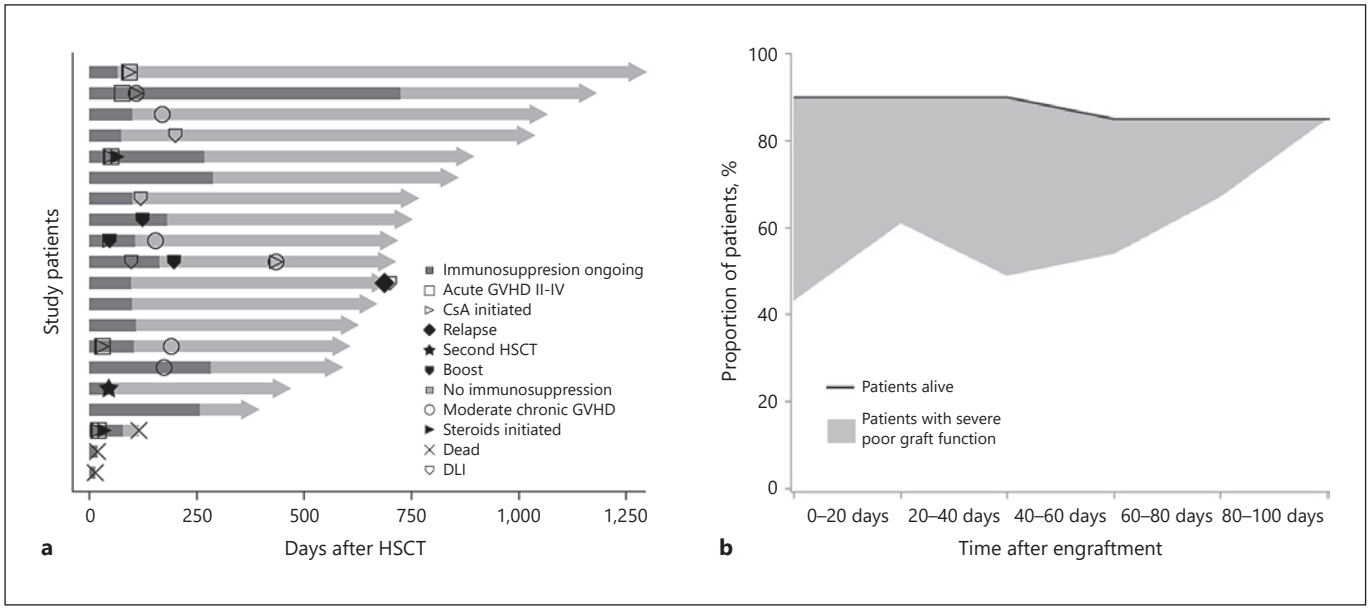

Fig. 1. Post-transplant outcomes (**a**) and dynamics of ruxolitinib concentration (**b**). **a** Swimmer plot of patients in the study in whom immunosuppression was continued or stopped. In 11 patients, who are alive and engrafted, ruxolitinib was discontinued at day+100. Four patients required continuation of ruxolitinib therapy due to moderate chronic GVHD. Three patients required CD34+ boost administration, and 3 required donor lymphocyte infusion to treat severe poor graft function. **b** The incidence of severe poor graft function was assessed after engraftment and was gradually resolved in all cases.

tion at day+100 (Fig. 1b, online suppl. Tables S3–4). Three patients required CD34+ boost administration and 3 required donor lymphocyte infusion to treat SPGF (Fig. 1a).

Mild VOD was observed in 1 patient. Sepsis was documented in 7 (35%) patients, and invasive mycosis was observed in 1 patient. Forty-five percent ($n = 9$) experienced viral reactivation or infection (CMV reactivation – 6, HHV type 6 – 3, HHV type 1, 2 – 2, BK – 1, parvovirus B19 – 1). Three patients experienced viral haemorrhagic cystitis (Table 2).

The incidence of acute GVHD grade II–IV was 25% ($n = 5$), and severe GVHD grade III–IV was 15% ($n = 3$). The overall rate of chronic GVHD was 40% ($n = 8$), moderate GVHD was 20% ($n = 4$), and mild GVHD was 20% ($n = 4$). Six patients were successfully treated with calcineurin inhibitors as a first-line therapy and 2 patients required systemic steroid therapy (Fig. 1a). One case of GVHD-related mortality was documented.

All engrafted patients achieved haematological and molecular remission and splenomegaly regression. Sixty-five percent of patients achieved near-complete bone marrow fibrosis resolution at day 398 (range 131–748). Molecular and haematological relapse was documented in 1 patient at day+665.

Analysis of C_{trough} concentrations of ruxolitinib demonstrated accumulation of the drug from day+7 (median 17.7 ng/mL) to day+14 (median 43.8 ng/mL, $p = 0.028$) and subsequent stable concentrations (Fig. 2b, online suppl. Table S1). The anticipated adverse effect of ruxolitinib on donor stem cells was eliminated by the drug intake interruption from day–1 to +4. Ruxolitinib was not detected in any samples at day 0. Ruxolitinib was abruptly discontinued before transplantation, but no withdrawal symptoms were registered.

Although the majority of patients in our study belonged to intermediate-2 and high DIPSS Plus risk groups, 2-year NRM was 15% (95% CI 4–34%), 2-year OS was 85% (95% CI 60–93%), and 2-year EFS was 72% (95% CI 45–87%) (Fig. 2a).

When the levels of inflammatory cytokines were analysed, we observed peaking levels after graft transfusion, with subsequent decline after PTCy and administration of ruxolitinib. In contrast, levels of IL-8 increased after engraftment, with no post-infusion peak. Positive correlation was documented between ruxolitinib concentration and IL-8 ($r = 0.242$, $p = 0.041$) and IL-1β ($r = 0.246$, $p = 0.039$) levels (online suppl. Fig. 1S, and online suppl. Table S2).

Table 2. Toxicity

Toxicity	Patients, *n* (%)
Hepatitis	
None	0
Grade 1	10 (50)
Grade 2	7 (35)
Grade 3	3 (15)
Mucositis	
None	2 (10)
Grade 1	12 (60)
Grade 2	3 (15)
Grade 3	3 (15)
Nephrotoxicity	
None	7 (35)
Grade 1	12 (60)
Grade 2	1 (5)
Neurotoxicity	
None	19 (95)
Grade 1	1 (5)
Severe sepsis	3 (15)
Invasive mycosis	1 (5)
VOD	
None	19 (95)
Mild	1 (5)
TMA	1 (5)
Haemorrhage	
Oesophageal varices haemorrhage	
Grade 3	1 (5)
Gastrointestinal haemorrhage grade 5	1 (5)
Haemorrhagic cystitis	
None	17 (85)
Grade 1	1 (5)
Grade 2	2 (10)

Gene expression levels of *STAT5B*, *JAK1*, and *JAK2* are presented in online supplementary Figure 1S and supplementary Table S2. A decline in expression was observed after HSCT for all three genes.

Discussion

In this study, we evaluated ruxolitinib as a bridge, relapse, and GVHD prevention agent in patients with MF. The regimen was well tolerated, with an acceptable rate of organ toxicity. CMV reactivation was documented in 30% of cases, which is similar to previous data with PTCy and tacrolimus-based prophylaxis [21]. However, in the previous studies, a higher incidence of CMV reactivation was reported when ruxolitinib was administered before alloHSCT with anti-thymocyte globulin (ATG) prophylaxis [22].

Acute GVHD grade III–IV was documented in 15% of patients. An advantage of our protocol is that the majority of patients were successfully treated with calcineurin inhibitors as a first-line therapy, with only 2 patients requiring systemic steroid therapy. Only one case of GVHD-related mortality was documented. Of note, the proportion of patients transplanted from human leukocyte antigen-mismatched unrelated or haploidentical donors was similar to that of the previous study, but we did not find increased rate of acute and chronic GVHD [13].

Our data revealed a moderate rate of PGF – 5%. Several other studies also reported low rates of PGF (4%) and did not find any association with ruxolitinib pre-treatment [23]. However, the prospective study by Gupta et al. [24] evaluating the safety and efficacy of pre-transplant ruxolitinib administration documented a significant rate of primary and secondary graft failures (16%) and organ toxicity (2-year NRM: 28%).

After ruxolitinib discontinuation, no withdrawal syndrome was observed. In contrast, a high incidence of ruxolitinib withdrawal syndrome was reported in the prospective JAK ALLO study [25]. However, in that study, ruxolitinib was stopped before the start of conditioning. In contrast, in our study, ruxolitinib was discontinued after the completion of conditioning, which seemed to prevent cytokine rebound syndrome.

In contrast to the rate of PGF, the incidence of SPGF was relatively high, and the median time to the leukocyte and platelet engraftment was relatively long. It should be noted that MF itself is associated with an increased risk of SPGF compared to other haematological disorders, with an SPGF rate of 17% in MF [26] versus 5–15% in other haematological disorders [27, 28]. In contrast to a previous study by Alchalby et al. [26], we did not exclude cases of SPGF associated with viral reactivation. This could partially explain the increased rate of SPGF in our study. A second possible reason for delayed engraftment is the inclusion of PTCy as a GVHD prophylaxis agent. Previous studies using PTCy in acute leukaemias reported a median time to neutrophil engraftment of 19 days, which is significantly higher than when an ATG-based regimen is used [21].

Due to the small number of cases and few events, it was impossible to correlate concentration of ruxolitinib and cytokine levels with clinical outcomes. Nonetheless, we evaluated the levels of inflammatory cytokines during

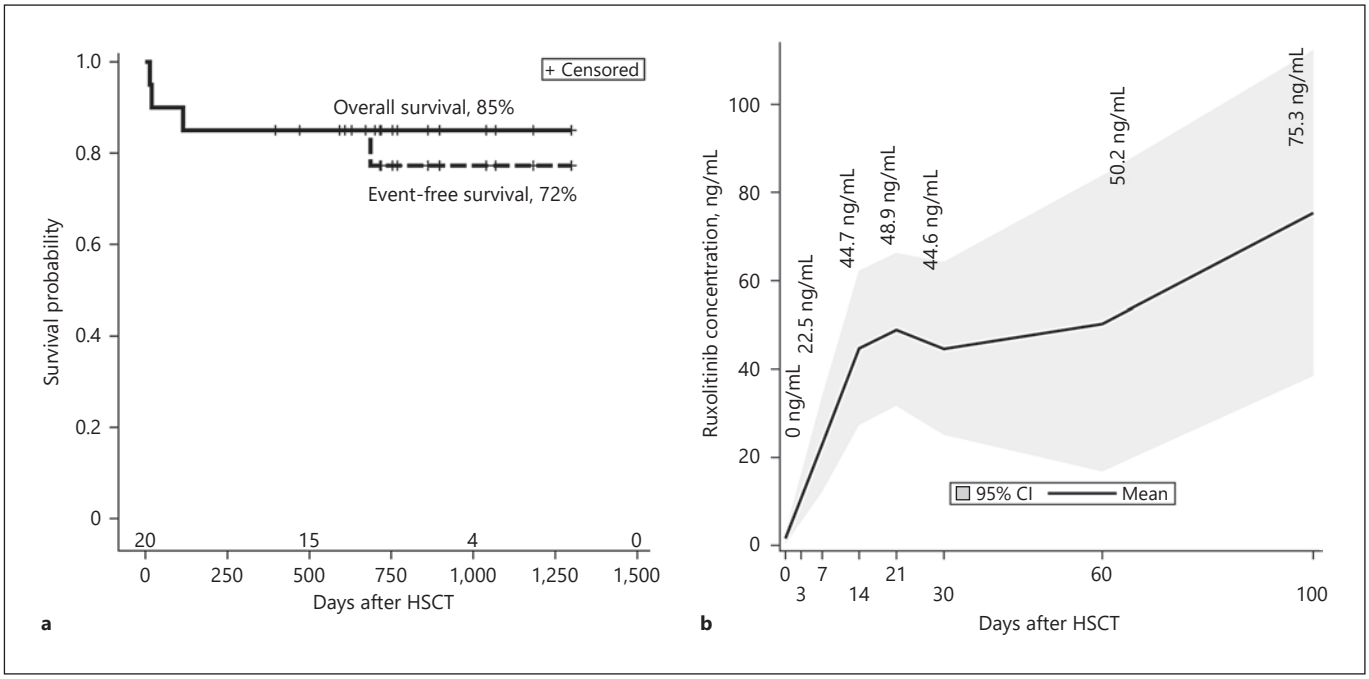

Fig. 2. a Two-year overall and event-free survival. **b** Ruxolitinib concentration.

ruxolitinib treatment to find general tendencies. Several previous reports showed that elevated plasma IL-8 is associated with decreased rates of acute [29] and chronic [6] GVHD, and we observed that high levels of IL-8 were linked with higher ruxolitinib concentrations. Therefore, stable ruxolitinib concentration after alloHSCT accompanied by elevated IL-8 might be associated with adequate GVHD control.

Although the majority of patients in our study belonged to the intermediate-2 and high DIPSS Plus risk groups, 2-year OS was 85% (95% CI 60–93%) and 2-year EFS was 72% (95% CI 45–87%). In contrast, the 2-year OS rates in the same DIPSS Plus risk groups without peritransplant ruxolitinib administration were only 40–50% [30].

Early relapse in MF patients is associated with poor prognosis. Ruxolitinib reduces tumour cell proliferation but does not eliminate tumour cells. However, the rate of relapse in our study was lower than previously reported and no early relapses were documented. This might be explained by augmented GVL effect after ruxolitinib [12] and PTCy [31]. Furthermore, no episodes of severe nephrotoxicity were observed, and a much lower rate of VOD was registered compared to ATG- [13] and PTCy-calcineurin inhibitor-based [21] GVHD prophylaxis. Thus, this new approach with ruxolitinib and PTCy might be a treatment option not only in MF, but also in other haematologic disorders.

The relatively high rate of SPGF should be taken into account, although it is possible that this could be mitigated by ruxolitinib dose reduction. The favourable toxicity profile and absence of early relapses prompted the initiation of a multicentre randomised phase II trial. The study will commence in the first quarter of 2020 and compare PTCy + ruxolitinib versus conventional PTCy + tacrolimus + mycophenolate mofetil prophylaxis in acute leukaemia patients undergoing unrelated and haploidentical transplantation.

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Statement of Ethics

The study was approved by the Local Ethical Committee of Pavlov First Saint Petersburg State Medical University. All patients signed the informed consent form.

Disclosure Statement

M.V.B. has received travel grants from Pfizer and Novartis and lecturer fees from Novartis and Celgene. I.S.M. has received travel grants from MSD, Novartis, Pfizer, Celgene, Takeda, and BMS, and consulting fees from Novartis and Celgene, Novartis. The remaining authors declare no competing financial interests.

Author Contributions

I.S.M., E.V.M., M.V.B., B.V.A. designed the study; M.V.B., I.S.M., E.V.M. wrote the manuscript; A.I.S, I.M.B. performed molecular analysis; E.A.S., S.V.L., G.G.R., V.V.B. performed histological examination and mass spectrometry analysis; T.A.R., J.J.V., E.I.D., S.N.B., A.L.A. conducted and supervised the study; S.I.M., B.V.A. revised the manuscript.

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