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ORIGINAL RESEARCH REPORT

Splenectomy following JAK1/JAK2 inhibitor therapy in patients with myelofibrosis undergoing allogeneic stem cell transplantation

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Abstract
Background: Allogeneic hematopoietic stem cell transplantation (alloHSCT) is the only treatment option with curative potential in patients with myelofibrosis (MF). The aim of our study was to evaluate the safety of splenectomy before alloHSCT in MF patients who failed to achieve significant spleen response after ruxolitinib therapy.
Methods: Splenectomy was performed in 12 patients for alloHSCT with myelofibrosis-primary (6 patients), post-polycythemia vera (3 patients). or postessential thrombocythemia (3 patients) between 2016 and 2018. The patients were prospectively included in the study if persistence of splenomegaly $\geq$ 25 cm was documented after at least 3 months of ruxolitinib therapy. In eight patients subsequent alloHSCT was performed.

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Results: Median length of hospital stay was 11 (8—30) days, median follow-up after splenectomy was 20.0 (0.6—31.1) months. No deaths were documented, perioperative morbidity was 50%. Three patients experienced portal vein thrombosis and one experienced splenic vein thrombosis. One patient developed pancreonecrosis and subdiaphragmatic abscess. Mean leukocyte count was significantly higher 1 month after splenectomy than before, 10.7 ± 1.7 versus 6.9 ± 2.3 × 109/L ($p = 0.03$). Platelets rate significantly elevated starting Day + 7 after splenectomy ($p = 0.01$). Median time between splenectomy and alloHSCT was 2.6 (0.17—4.5) months. All patients achieved engraftment. In early posttransplant period no cases of severe sepsis, intraabdominal infections were documented. One patient died after alloHSCT due to thrombotic microangiopathy. Seven patients are alive in disease complete remission. No relapses after alloHSCT were observed. Two-year overall survival in the whole group is 90% (95%CI 98—43%).

Conclusion: Splenectomy before alloHSCT might be a promising option in patients who failed to achieve significant spleen response after ruxolitinib therapy.

Introduction

Primary, postpolycythemia, and postessential thrombocythemia myelofibrosis (MF) are chronic BCR/ABL-negative myeloproliferative neoplasms characterized by extramedullary hematopoiesis, circulating CD34+ progenitor cells, bone marrow fibrosis, elevation of proinflammatory cytokines [1,2] and usually progressive disease course [3]. Allogeneic hematopoietic stem cell transplantation (alloHSCT) is the only treatment option with curative potential in MF [4]. AlloHSCT is indicated in patients with intermediate-2 and high risk by dynamic international prognostic scoring system plus (DIPSSplus) younger than 65 years [5]. Most of the transplant candidates have significant tumor burden. Massive splenomegaly (>15 cm under left costal margin) is documented in 53—77% of cases and might be associated with unfavorable outcome [6,7], severe poor graft function [8], and primary graft failure possibly due to deposition of donor stem cells in enlarged spleen [9], Novel target therapy with Janus kinase 1/2 (JAK1/JAK2) inhibitors significantly reduces palpable spleen in at least 50% of MF-patients [10]. But ~30% of patients do not achieve adequate spleen response and massive splenomegaly is still present at the time of alloHSCT [11]. In this group of patients splenectomy before alloHSCT might be an option. The broad use of splenectomy was limited due to perioperative morbidity and mortality [12]. However, in the absence of profound spleen response after JAK1/JAK2 inhibitor administration splenectomy might be considered as a part of pretransplant bridge therapy. The aim of our study was to evaluate the safety of splenectomy before alloHSCT in MF patients who failed to achieve significant spleen response after ruxolitinib therapy.

Materials and methods

Patient selection

Splenectomy was performed in 12 patients for alloHSCT at the Pavlov First Saint Petersburg State Medical University, Saint-Petersburg, Russia in the time period 2002—2018 (Table 1). Six patents were diagnosed with primary myelofibrosis, three with postpolycythemia vera myelofibrosis and three with postessential thrombocythemia myelofibrosis according to the World Health Organization criteria of 2016 [13]. Ten patients had intermediate-2 and two had high DIPSSplus risk [14]. The indication for splenectomy was persistence of splenlomegaly ≥25 cm in maximal size according to ultrasound or computer tomography data after at least 3 months. All patients received ruxolitinib 30—45 mg daily. Response to JAK1/JAK2 inhibitor therapy was assessed according to European Leukemia Net criteria [15]. Ten patients achieved disease stabilization and two achieved clinical improvement. Two patients experienced Grade 2 thrombocytopenia. Toxicity was assessed with Common Terminology Criteria for Adverse Events version 4.03. Six patients were red blood cells transfusion dependent. All patients had symptomatic splenomegaly. All patients gave written informed consent and the study was approved by the Pavlov First Saint Petersburg State Medical University local ethic committee.

Surgical technique and postoperative management

Due to large splenomegaly in all cases open splenectomy was performed. Midline incision was the preferred access in all cases. The spleen was mobilized initially and ligation of hilar vessels was performed. In all cases a drain was placed in the splenic bed. All patients received standard perioperative antibiotic prophylaxis. Anticoagulant therapy was administered from Day + 1 until Day + 7 in the postoperative period; antiaggregant therapy and ruxolitinib was administered from Day + 3 until the start of the conditioning regimen. Operating time, blood loss, intraoperative transfusion data, and splenic weight were noted at the end of each case. Removed spleens were sent for histological examination.

In eight patients subsequent alloHSCT was performed. In four other patients alloHSCT is planned. Reduced intensity conditioning was performed according to the protocol by Kröger et al. [16] and consisted of fludarabine 180 mg/m^2 and busulfan 10 mg/kg. Graft versus host disease (GVHD) prophylaxis was performed according to the protocol by Luznik et al. [17] and included posttransplant cyclophos-

Table 1 Patient characteristics.

Characteristic	Value
Median age, y (range)	56 (32—64)
Sex, M/F	5/7
Diagnosis	
Primary myelofibrosis	6
Post-polycythemia vera myelofibrosis	3
Post-essential thrombocythemia myelofibrosis	3
Risk profile according to DIPSSplus	
Intermediate-2	2
High	10
Palpable spleen size median, cm (range)	20 (6—25)
Fibrosis grade before splenectomy	
MF-2	2
MF-3	10
Mutational status	
JAK2V617F-positive	7
CALR-positive	5
Karyotype	
Normal	7
Del(20q)	2
del(13q21)	1
del(6q)	1
Unknown	1
Median leukocyte, $\times 10^9$/L (range)	5.5 (1.8—30.0)
Median platelet, $\times 10^9$/L (range)	132 (33—413)
Median hemoglobin, × g/L (range)	78 (64—109)
Median time of ruxolitinib therapy, mo (range)	8.9 (5.4—14.5)
Disease response at the time of splenectomy (ELN criteria)	
Clinical improvement	2
Stabilization	10

DIPSSplus = dynamic international prognostic scoring system plus; ELN = European Leukemia Net; MF = myelofibrosis; mo = month, y = year.

phamide 50 mg/kg/daily at Days + 3 and + 4. Time to engraftment was calculated as time from HSCT to unsupported neutrophil count > 500/μL and white blood cell count > 1000/μL for 3 consecutive days. Primary graft failure was defined as the complete absence of donor chimerism in bone marrow aspirate by Day + 40. Disease staging, including bone marrow aspirate, was routinely performed on Days + 30, +60, +100, +180, and + 365 posttransplant. Trephine bone marrow biopsy was performed on Days + 60, +100, +180, and + 365 to evaluate bone marrow fibrosis regression [18].

Statistical analysis

Statistical comparisons were performed using the Wilcoxon matched pairs test for continuous variables. Results were reported as medians or means standard error of the mean, with statistical significance at $p < 0.05$. The survival distributions for overall survival (OS) were calculated using Kaplan—Meier methodology with 95% confidence intervals (CI).

Results

Operative data and postoperative course

Median length of hospital stay was 11 (8—30) days and median follow-up after splenectomy was 20.0 (0.6—31.1) months. During this period no deaths were documented. The mean operative time was 170 (range 90—250) minutes and the average blood loss was 580 (range 200—1500) mL. All patients required intraoperative red blood cell transfusion, and one patient was treated with intraoperative platelet transfusion. Perioperative morbidity was 50%. Four patients experienced portal vein and one experienced splenic vein thrombosis. Median time to thrombosis was 8 (5—23) days. In three patients thrombosis was symptomatic and accompanied by fever and C-reactive protein elevation with a median of 130 (range 88—165) mg/L and required antibacterial therapy modification. In four patients subsequent oral anticoagulant therapy was administrated until the start of the conditioning regimen. One patient developed pancreonecrosis and subdiaphragmatic abscess. During the second laparotomy necrotic tissues were removed and infection was completely resolved after antibacterial therapy. The median weight of the removed spleens was

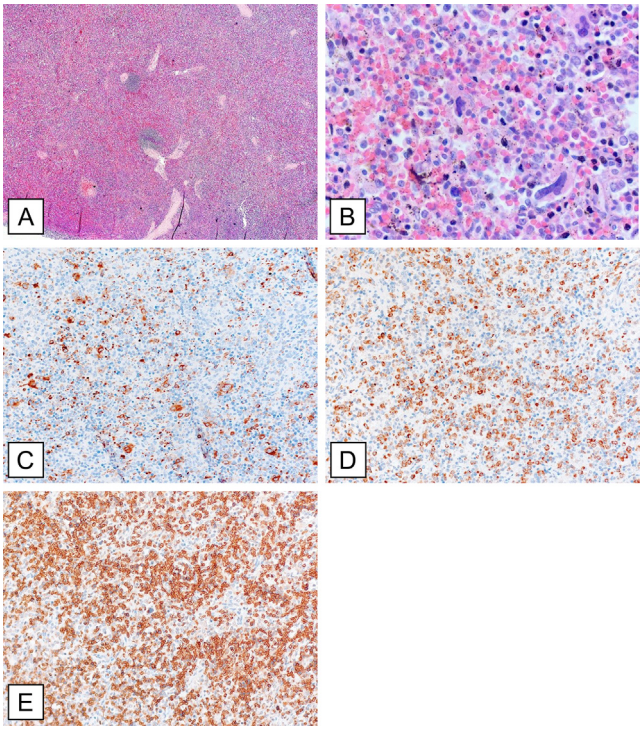

Fig. 1 Microscopic picture of the spleen removed following unsuccessful ruxolitinib therapy. (A) Expansion of the red pulp. Two atrophic follicles seen in the center. Hematoxylin and eosin (HE), ×40; (B) three-lineage hematopoiesis with atypical megakaryocytes. HE, ×400; (C) megakaryocytes at different stages of maturation, highlighted by stain for CD61. Immunoperoxidase stain, ×100; (D) cells of granulocytic lineage dispersed in the red pulp. Immunoperoxidase stain with antibodies against myeloperoxidase, ×100; and (E) cells of erythroid lineage, lying in clusters in the red pulp. Immunoperoxidase stain with antibodies against glycophorin A = ×100.

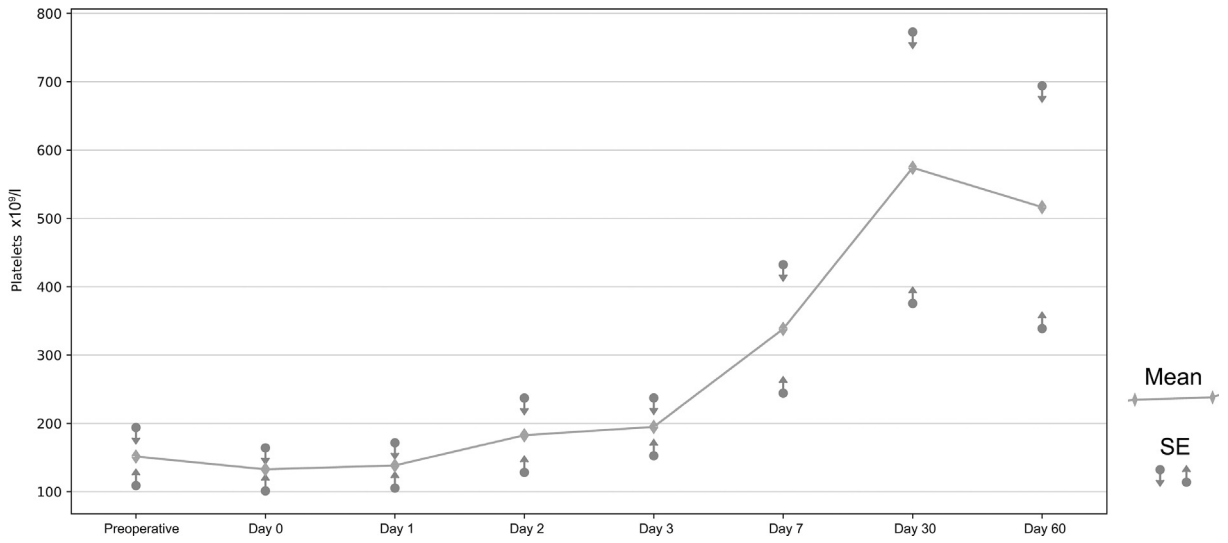

Fig. 2 Dynamic of platelet count after splenectomy. Mean platelet count was significantly higher at Day + 7 ($p = 0.01$), Day + 30 ($p = 0.01$), and Day + 60 ($p = 0.02$) after splenectomy than before. SE = standard error.

2.2 (1.5—4.5) kg and the median size was 327 (112—600) cm^2. According to histological examination spleen myeloid metaplasia was present in all patients even after ruxolitinib therapy (Fig. 1). Mean leukocyte count was significantly higher 1 month after splenectomy than before splenectomy (10.7 ± 1.7 versus $6.9 \pm 2.3 \times 109/L$; $p = 0.03$). Platelets rate was significantly higher starting Day + 7 after splenectomy than preoperative ($p = 0.01$; Fig. 2).

Posttransplant outcomes

In eight patients alloHSCT was performed; four patients are alive and awaiting alloHSCT. The median time between splenectomy and alloHSCT was 2.6 (0.17—4.5) months. All patients achieved engraftment; one patient achieved engraftment after the second alloHSCT. The median time to leukocyte engraftment was 35 (20—58) days and to platelet engraftment was 34 (15—57) days. Four patients developed severe poor graft function, which resolved spontaneously in all patients. In the early posttransplant period no case of severe sepsis or intra-abdominal infection were documented. One patient died after alloHSCT due to thrombotic microangiopathy. Seven patients are alive and in complete disease remission. No relapses after alloHSCT were observed. All patients achieved hematological, molecular remission, and full donor chimerism. Six patients experienced bone marrow fibrosis regression (Table 2). Two-year overall survival in the whole group is 90% (95% CI 98—43%; Fig. 3).

Table 2 Transplant characteristics and outcomes of eight patients proceeded to alloHSCT.

Characteristic	Value
Median follow-up after alloHSCT, mo (range)	19 (4—31)
Median CD34 + cells/kg $\times 10^6$ (range)	7.5 (1.4—12.0)
Donor (no. of patients)	
Human leukocyte antigen-identical sibling	2
Haploidentical	3
Unrelated	3
Time to leukocyte engraftment, median, d (range)	35 (20—58)
Time to platelet engraftment, median, d (range)	34 (15—57)
Acute GVHD (no. of patients)	
Grade 2—4	3
Grade 3—4	2
Chronic GVHD, National Institutes of Health (no. of patients)	
Moderate	1
Severe	0
Molecular remission (no. of patients)	8
Hematological remission	8
Full donor chimerism	8
Bone marrow fibrosis regression	6
Relapse	0
Alive (no. of patients)	7
Died	1

alloHSCT = allogeneic hematopoietic stem cell transplantation; d = days; GVHD = graft versus host disease; mo = months.

Discussion

To our knowledge this is the first report regarding the use of splenectomy as a bridge to alloHSCT in patients with MF who failed to achieve spleen response after JAK1/JAK2 inhibitor therapy. Although sample size is small several observations could be made concerning the place of splenectomy after unsuccessful ruxolitinib pretreatment.

The impact of splenomegaly on the results of alloHSCT is currently uncertain. Myeloproliferative neoplasms are characterized by increased risk of primary graft failure when compared with other hematologic malignancies, for example acute myeloid leukemia 11% and 4% respectively [19].

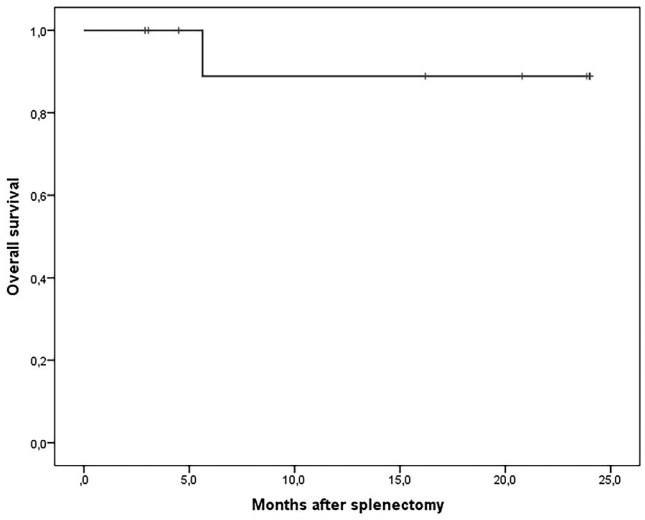

Fig. 3 Two-year overall survival after splenectomy and alloHSCT. alloHSCT = allogeneic hematopoietic stem cell transplantation.

Olsson et al. [19] found the risk of primary graft failure was dependent on spleen status and presence of splenomegaly. Large splenomegaly is linked with poor prognosis [6] and higher risk of poor graft function [8]. The one reason for that might be pooling of donor cells in the enlarged spleen [9]. Thereby splenectomy might be an option to reduce tumor burden before alloHSCT and improve transplant outcome in MF. The only target drug that significantly reduces tumor burden and splenomegaly in MF is JAK1/JAK2 inhibitor ruxolitinib. In our study 12 patients did not achieve profound spleen response after at least 3 months of ruxolitinib therapy. To reduce tumor burden before alloHSCT we performed splenectomy. Although splenectomy in myeloproliferative disorders is associated with relatively high perioperative mortality ~9% [12], there were no deaths in the early postoperative period according to our data. The most frequent complication was venous thrombosis which usually occurred 8 days after splenectomy. In most cases it was symptomatic and accompanied with fever and C-reactive protein elevation. It should be noted that pH-negative myeloproliferative neoplasms are associated with a high risk of venous thrombotic events. Qualitative abnormalities, elevated platelet and leukocyte count and prothrombotic microenvironment are likely to play a key-role in myeloproliferative neoplasm thrombophilia [20]. According to our and literature data ~50% of patients after splenectomy experience marked platelet and leukocyte elevation which is documented usually in the first days after splenectomy [21,22]. It might be an additional factor that increases thrombotic risk. Thus all patients in our study received anticoagulant and antiaggregant prophylaxis. However, despite this, four out of 12 patients experienced thrombotic events. Several studies reported venous thromboembolism in 9—16% of patients [21,23] but there are no randomized trials evaluating efficacy of anticoagulant prophylaxis. According to meta-analysis performed by Zhang et al. [23] the incidence of venous thrombosis was significantly reduced in the prophylactic anticoagulation group compared with the control group. Although there are no standard anticoagulant prophylaxis regimens, it might be an effective option to prevent thrombosis. Infections are also a common complication after splenectomy and are documented in ~9% of cases [24]. In our study only one patient developed pancreonecrosis and subdiaphragmatic abscess. That patient required a second laparotomy and the condition resolved after administration of antibacterial therapy.

In analyzing posttransplant outcomes of eight patients we found no case of severe sepsis or intra-abdominal infection. In all but one patient engraftment was documented after the first alloHSCT. Currently the role of splenectomy before alloHSCT remains unclear. Some of the studies showed an increased rate of relapse in the case of splenectomy [16]. In the other retrospective reports survival advantage was documented after alloHSCT in splenectomized patents [25]. Nevertheless, splenectomy is associated with early neutrophil and platelet engraftment and reduced transfusion dependency [7] but splenectomy is not the standard of care in alloHSCT candidates even in patients with huge splenomegaly [5]. It should be noted that in our study the median time between splenectomy and alloHSCT was very short at 2.6 months. We found only one study evaluated this characteristic. Robin et al. [25] reported a median of 2 months between splenectomy and alloHSCT. Their study documented the beneficial impact of splenectomy on overall and event-free survival. This fact might be important because after splenectomy the patients are more likely to develop hepatic involvement and failure and acute myeloid leukemia evolution [12,26]. Long periods between splenectomy and alloHSCT possibly mitigate the beneficial effect of splenectomy in terms of tumor burden reduction. Thereby previous studies might not show survival advantage in splenectomized patients.

JAK1/JAK2 inhibitor ruxolitinib is an effective bridge-therapy in patients with MF undergoing alloHSCT. In some patients significant spleen response is not achieved. Splenectomy might be a promising additional therapeutic option in this subset of patients. Larger studies are needed to confirm this assumption.

Acknowledgments

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Conflicts of interest

Authors declare no conflicts of interests.

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