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The Impact of Splenectomy in Myelofibrosis Patients before Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Performing a pretransplantation splenectomy in patients with myelofibrosis (MF) is a matter of debate, as while the procedure improves hematological recovery, it may lead to severe morbidities. We retrospectively analyzed data from 85 consecutive patients who underwent transplantation in our center for MF, including 39 patients who underwent splenectomy before their transplantation. A majority of them had primary MF (78%), were considered high-risk patients (84% dynamic international prognostic scoring system intermediate-2 or higher), and had received transplants from HLA-matched sibling donors (56%) after a reduced-intensity conditioning regimen (82%). One-half of all splenectomized patients presented surgical or postsurgical morbidities, most frequently thrombosis and hemorrhage. After adjustment using Cox models, pretransplantation splenectomy was not associated with nonrelapse mortality or post-transplantation relapse but with an improved overall survival (OS) and event-free survival (EFS). We conclude that some patients with huge splenomegaly may undergo pretransplantation splenectomy without a deleterious impact on post-transplantation outcomes. OS and EFS improvement should in confirmed in controlled study.

INTRODUCTION

Splenectomy to improve outcomes in patients who undergo transplantation with myeloproliferative neoplasia (MPN) is currently a matter of debate, and conflicting results have been reported. In the 1980s, pretransplantation splenectomy was regularly performed on MPN patients with massive spleens to limit tumor burden and engraftment failure [1-5]. Schmitz et al. reported that the spleen may act as a reservoir for malignant cells, increasing post-transplantation relapse risks and disease progression [1]. Conversely, splenectomy has also been reported to be associated with high morbidity and mortality in patients with hematological malignancies: Barosi et al. reported that among 71 patients with primary myelofibrosis (MF), 8.4% died and 39.3% experienced severe complications after splenectomy [6]. Lafaye et al. also reported mixed results for 39 MF patients splenectomized between 1980 and 1993 at Saint-Louis Hospital, APHP, Paris [7]. Although hematological improvement was observed in 60% of cases, 33 patients (85%) presented serious complications and 5 (13%) of them died [7]. Barosi et al. reported that splenectomy was significantly and independently associated with a higher risk of blast transformation in a very large retrospective cohort of patients (n = 549) with MF [8]. The aim of splenectomy in these cases was not curative but rather to improve patient comfort, either by decreasing anemia and thrombocytopenia or by relieving spleen pain or other complications arising from splenomegaly. Splenectomy is often 1 of the palliative treatments proposed after the failure of other therapies. The conclusions of this paper cannot be applied to patients who undergo transplantation after splenectomy, because transplantation itself should have an impact on outcome, and the delay between splenectomy and transplantation is usually short. In the transplantation setting, shorter post-transplantation hematological recovery has regularly been reported in splenectomized patients, along with substantial better graft function in patients splenectomized after transplantation, but the influence on post-transplantation survival or relapse is more controversial [9-11]. Kröger et al.

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have described more relapses in splenectomized patients, while the Société Française de Greffe de Moelle et de Thérapie Cellulaire has reported that survival was better in splenectomized male patients [12,13].

In this paper, we report on all the patients with MF who underwent hematopoietic stem cell transplantation (HSCT) in our department, before analyzing the potential impact that splenectomy had on them, as well as splenectomy-related complications.

METHOD

We enrolled in our study all consecutive patients who underwent transplantation in our center from June 1988 to December 2014 for primary MF or MPN evolving to MF. Patients included into the "JAK-ALLO" ongoing trial were excluded (https://clinicaltrials.gov Identifier: NCT01795677). All patients gave their informed consent for clinical research in line with the Helsinki Declaration. Data were extracted from the Promise registry before being completed and double-checked by 2 investigators.

Graft-versus-host disease (GVHD) occurring before post-transplantation day 120 was considered to be acute, whereas GVHD occurring after day 120 was considered to be chronic. Events used to estimate overall survival (OS) and event-free survival (EFS) were death and disease relapse followed by death, respectively. *Hematological engraftment* was considered within the first 60 days after transplantation for neutrophil and before day 100 for platelet transfusions. The date of *neutrophil recovery* was defined as the first of 3 consecutive days with neutrophil of more than .5 g/L. The date of *platelet recovery* was defined as the first of 7 consecutive days with more than 20 g/L, without transfusion. *Graft loss* or *rejection* were defined by pancytopenia associated with very poor cellularity in the marrow and the absence of donor engraftment (confirmed by molecular chimerism).

Summary statistics—median, interquartile range, and percentages—are reported below. Comparisons between the characteristics of splenectomized patients and those who were not were made using the Wilcoxon rank-sum test and Fisher's exact test. Cumulative incidence of acute and chronic GVHD, neutrophil and platelet recovery, and relapse were computed in a competing risk framework because of deaths occurring before the events of interest, before comparisons were made concerning splenectomy using the Gray test. OS and EFS were estimated using the Kaplan-Meier method, before comparisons were made concerning splenectomy using the log-rank test.

Univariate Cox regression models for EFS were then fitted, with the strength of association between baseline characteristics and event hazards measured by hazard ratio (HR) with 95% confidence intervals (CI). Variables tested in the univariate analysis were patient and donor age, patient and donor sex, type of transplantation (HLA identical or not), patient and donor cytomegalovirus (CMV) serology, ABO blood group incompatibility, comorbidity score, disease (primary or secondary MF), severity of disease as measured by the dynamic international prognostic scoring system [14] (DIPSS), time from diagnosis to transplantation, pregraft treatment, conditioning regimen (reduced or not), in vivo T cell depletion, and GVHD prophylaxis. All variables associated with the outcome at the 10% level were introduced in a multivariate Cox model with stepwise selection procedure. Similar analysis was performed to predict the occurrence of deaths, whatever their causes.

Analysis of the prognostic factors for the cause-specific hazards of relapse and nonrelapse mortality (NRM) used Cox models, with similar univariate then multivariate modeling strategies.

Statistical tests were 2-sided, with P values of .05 or less denoting statistical significance. Analysis was performed using R software (https://www.R-project.org/).

RESULTS

Patient Characteristics

Eighty-five patients were included in this retrospective study: 39 of them were splenectomized before transplantation. Clinical characteristics were broadly similar between splenectomized and nonsplenectomized patients, except that no splenectomized patients developed acute myeloblastic leukemia (AML) (Table 1). The median age was 52.5 years in nonsplenectomized patients versus 54 years in splenectomized patients. The primary diagnosis was primary MF for 35 (76%) of the nonsplenectomized patients and 31 (79%) of the splenectomized patients. Time from initial diagnosis to transplantation was not significantly shorter in nonsplenectomized patients (556 days versus 1154 days). MF evolved into AML in 6 nonsplenectomized patients and none of the splenectomized patients (but 7 splenectomized patients had CD34-positive infiltration > 5% in the spleen). At the time of transplantation, and with blastic phase considered to be a high risk, DIPSS was intermediate-2 or higher in 39 (85%) of the nonsplenectomized patients and 32 (82%) of the splenectomized patients. Intensive chemotherapy was given to 4 patients (2 nonsplenectomized and 2 splenectomized), either because of blastic phase or just before splenectomy to reduce the tumor burden. Only 2 patients received JAK inhibitors, all of them in the nonsplenectomized group. Donor types for nonsplenectomized and splenectomized patients, respectively, were HLA-matched related donors in 26 (56%) and 21 (54%), HLA-matched unrelated donors in 7 (15%) and 9 (23%), and HLA-mismatched unrelated donors in 13 (28%) and 8 (20%). Conditioning regimen was mostly reduced intensity (78% in nonsplenectomized versus 87% in splenectomized) without T cell depletion (80% in nonsplenectomized versus 85% in splenectomized). Fourteen nonsplenectomized patients had a massive splenomegaly (≥ 20 cm), 15 had a spleen size between 15 cm and 20 cm, and 17 patients had no splenomegaly.

Pretransplantation Splenectomy

Thirty-nine patients were splenectomized to manage the disease at a median of 58 days before transplantation (Table 2). Spleen histology was not available for 1 patient. The median weight of the spleen was 1950 grams. Median hospitalization duration was 9 days, but 4 out of 39 patients were readmitted after discharge to be treated for secondary complications. The most frequent complications occurring after surgery were hemorrhage in 14 patients, venous splenoportal thrombosis in 12 patients, and profound abscesses in 2 patients. Seven patients required new surgery for complications: 2 for intestinal occlusion, 4 for hemorrhages, and 1 for an abscess. Two patients were transferred to intensive care. Nineteen (50%) patients had at least 1 complication. Six patients experienced both hemorrhage and thrombosis complications. Complications were not more frequent according to age (51 years in patients with or without complications), spleen weight (mean, 2378 versus 2141 grams), $CD34^+$ splenic cells (>5% for 2 of 19 patients with complications versus 5 of 19 patients without complications), or DIPSS (int-2 or higher in 17 of 19 patients with complications or without complications).

Engraftment and GVHD

One nonsplenectomized patient had early graft rejection and 1 splenectomized patient had late rejection. Median time to neutrophil engraftment was 18 days in nonsplenectomized patients and 14 days in splenectomized patients. The cumulative incidence of neutrophil engraftment at day 60 was 98% in nonsplenectomized and 92% in splenectomized ($P = .089$). Median time to platelet engraftment was 19 days in nonsplenectomized and 14 days in splenectomized. The cumulative incidence of platelet recovery by day 100 was 78.3% in nonsplenectomized and 82.1% in splenectomized ($P = .26$). Cumulative incidence of grade II to IV acute GVHD at day 120 was 72% in nonsplenectomized and 58% in splenectomized ($P = .41$), whereas extensive chronic GVHD at 1 year was 43.5% in nonsplenectomized and 56.4% in splenectomized ($P = .19$). The cumulative incidences of hematological recovery and GVHD are shown in Figure 1.