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Influence of Previous Inflammatory Bowel Disease on the Outcome of Allogeneic Hematopoietic Stem Cell Transplantation: A Matched-Pair Analysis

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A B S T R A C T

The idiopathic inflammatory bowel diseases (IBDs) Crohn's disease and ulcerative colitis are associated with increased risk of hematologic malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) could be a curative strategy in this setting, but has been thought to be associated with increased nonrelapse mortality (NRM). We conducted a national French retrospective analysis of patients with IBD who underwent allogeneic HSCT for hematologic malignancies and were matched with 3 controls according to recipient, donor, and transplant characteristics. Between 2004 and 2015, 18 patients with IBD underwent allogeneic HSCT. With a median follow-up of 33 months for the patients with IBD and 57 months for controls, the cumulative incidence of grade II-IV acute graft-versus-host disease (GVHD) was 39% for the patients with IBD and 40% for controls (hazard ratio [HR], 1.10; $P = .82$). The cumulative incidence of chronic GVHD at 48 months was 52% for the patients with IBD and 43% for controls (HR, 0.92; $P = .89$). Nonrelapse mortality at 48 months was 19% for the patients with IBD and 11% for controls (HR, 4.93; $P = .067$). Overall survival at 48 months was 59% for the patients with IBD and 60% for matched controls (HR, 1.35; $P = .56$). In conclusion, IBD should not be considered a contraindication for transplantation, and its impact on comorbidity indexes should be reduced.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBDs), with an incidence of 8 to 14 per 100,000 and a prevalence rate of 120 to 200 per 100,000 for CD and an incidence of 6 to 15 per 100,000 and a prevalence rate of 50 to 200 per 100,000 for UC in Western countries [1]. CD is characterized by ulcerative bowel lesions that can occur in the entire gastrointestinal tract with interspaces of normal mucosa between the ulcerations, whereas in UC, ulcerations are continuous and affect only the colon.

Dysregulation of the immune response favored by genetic predispositions and environmental factors are implicated in the pathogenesis of IBD. Therapy for IBD, including nonsteroidal anti-inflammatory drugs, glucocorticoids, anti-tumor

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necrosis factor (TNF), and azathioprine, aims to decrease the flares of inflammation and slow the evolution of disease by modulating the immune system, but are not curative. Autologous hematopoietic stem cell transplantation (HSCT) has been advocated for severe cases [2].

Inflammatory bowel diseases have been associated with an increased risk of intestinal cancers and hematologic malignancies [3]. These later malignancies, including lymphoma and leukemia, can be triggered by chronic inflammation or induced by IBD treatment. These secondary hematologic malignancies are associated with a dismal prognosis, and allogeneic HSCT is often considered as a therapeutic option.

IBDs are thought to increase the risk and the severity of graft-versus-host disease (GVHD) after allogeneic HSCT, resulting in increased nonrelapse mortality (NRM). Thus, IBD before allogeneic HSCT has been considered to increase comorbidity risk scores, such as the HSCT comorbidity index described by Sorror et al. [4]. To assess the outcome of patients with IBDs after allogeneic HSCT, we designed a nationwide French retrospective case-controlled analysis. The aim was to compare the incidence of GVHD, the incidence of NRM, and overall survival in the 2 groups of patients.

MATERIALS AND METHODS

Study Population

All French transplantation centers were searched though the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire for patients age ≥18 years with previous IBD (CD or UC) who underwent allogeneic HSCT between January 2004 and December 2015 for a hematologic malignancy. Patient clinical and biological data were abstracted from the prospective ProMISE database, and additional data were collected through a special questionnaire. Each patient with IBD was paired with 3 controls matched for the following factors: center, sex, age at transplantation, disease, intensity of conditioning, HLA disparity between donor and recipient, donor type (related or unrelated), stem cell source, and period of transplantation. The incidence of GVHD, incidence of NRM, and overall survival were compared between the 2 groups.

Acute GVHD was diagnosed and scored according to the International Bone Marrow Transplant Registry and Glucksberg criteria. Patients who developed acute GVHD were treated with methylprednisolone (1 to 2 mg/kg/day). Chronic GVHD was staged according to the National Institutes of Health criteria. NRM was defined as any death occurring during continuous complete remission.

Statistical Analysis

All time-to-event outcomes were counted from the date of transplantation to the date of event or the date of last follow-up, except for acute GVHD, which was arbitrarily censored at 100 days. NRM was defined as death by any cause occurring before disease relapse/progression. Death was considered a competing event for GVHD, and NRM and relapse/progression were considered mutually competing risks. Overall survival curves were estimated using the Kaplan-Meier product-limit estimator. For competing risk analyses, cumulative incidence functions were estimated using the usual methodology. Group comparisons were done using stratified Cox proportional hazard models for overall survival and stratified cause-specific proportional hazards models for NRM and chronic GVHD. For acute GVHD, a stratified proportional subdistribution hazard was used [5]. All tests were stratified on the matched set (1 patient with IBD matched with 1 to 3 controls). A P value $< .05$ was considered statistically significant. All statistical analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

Between 2004 and 2015, 18 patients with IBD (13 with CD and 5 with UC) underwent allogeneic HSCT for a hematologic malignancy (Table 1). The cohort comprised 6 females and 12 males, with a median age of 49 years (range, 38 to 55 years) at the time of transplantation. Eight patients with IBD (44%) underwent transplantation between 2006 and 2010, and 10 patients (56%) did so between 2011 and 2015. The most frequent malignancies in the IBD group were acute leukemia (9 patients; 50%) and myelodysplastic/myeloproliferative neoplasm (7 patients). The donor was an identical sibling for 10 patients (56%), and a matched unrelated donor for 6 patients (33%). Eleven patients received a reduced-intensity conditioning (RIC) regimen and 7 patients received a myeloablative conditioning regimen. There were no differences in antimicrobial prophylaxis, GVHD prophylaxis, and supportive measures between the 2 groups. There was no statistical difference between the IBD and control groups at baseline (Table 1).

Table 1
Baseline Patient Characteristics

Variable	IBD Group (n = 18)	Control Group (n = 50)	*P* Value
Sex, n (%)			.89
Female	6 (33)	18 (36)	
Male	12 (67)	32 (64)	
Age at transplantation, yr, median (IQR)	49 (38-55)	49 (37-54)	.62
Disease, n (%)			>.99
Acute leukemia	9 (50)	30 (60)	
Myelodysplastic syndrome/myeloproliferative neoplasms	7 (39)	14 (28)	
Non-Hodgkin lymphoma	1 (6)	3 (6)	
Multiple myeloma	1 (6)	3 (6)	
Transplantation period, n (%)			.88
2006-2010	8 (44)	24 (48)	
2011-2015	10 (56)	26 (52)	
Donor type, n (%)			*
Identical sibling	10 (56)	30 (60)	
Matched unrelated	6 (33)	14 (28)	
Mismatched relative	1 (6)	3 (6)	
Mismatched unrelated	1 (6)	3 (6)	
Stem cell source, n (%)			>.99
Peripheral blood	15 (83)	42 (84)	
Bone marrow	2 (11)	5 (10)	
Cord blood	1 (6)	3 (6)	
Conditioning, n (%)			*
Reduced-intensity conditioning	11 (61)	31 (62)	
Myeloablative conditioning	7 (39)	19 (38)	
Total body irradiation >2 Gy, n (%)	3 (17)	11 (22)	.44
Antithymocyte globulin use, n (%)	9 (50)	21 (42)	.45
CD34 cells in graft, $\times 10^6$/kg, median (IQR)	5.5 (2.7-8.2)	5.1 (4.0-8.0)	.85
Number missing	0	1	
Donor age, yr, median (IQR)	43 (33-49)	41 (28-53)	.48
Donor/recipient sex match, n (%)			.92
Female/female	2 (11)	9 (18)	
Female/male	4 (22)	12 (24)	
Male/female	4 (22)	9 (18)	
Male/male	8 (44)	20 (40)	
Donor/recipient cytomegalovirus serostatus, n (%)			.42
Negative/negative	9 (50)	17 (35)	
Negative/positive	3 (17)	7 (14)	
Positive/negative	3 (17)	9 (18)	
Positive/positive	3 (17)	16 (33)	
Number missing	0	1	

IQR indicates interquartile range.
Each case was matched to 3 controls, except for 2 cases for which only 1 match was found. Thus, percentages may thus appear different even in cases of perfect matching.
* Exact matching.

Treatment Outcomes

The median follow-up was 33 months for the IBD group and 57 months for controls. Acute GVHD grade II-IV occurred in 7 patients (6 skin, 3 gut, and 2 liver grade II-IV acute