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Donor Lymphocyte Infusion May Reduce the Incidence of Bronchiolitis Obliterans after Allogeneic Stem Cell Transplantation

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Bronchiolitis obliterans (BO) is a serious pulmonary complication after allogeneic hematopoietic stem cell transplantation (HSCT). The aim of this study was to evaluate the diagnostic methods used, the incidence of BO, risk factors, and outcome in patients with BO at our center. The study included 527 HSCT patients transplanted between 1995 and 2003. Lung function tests (n = 1177) and risk factor analyses were performed in all patients. Chest X-rays and high-resolution tomographies were investigated in patients with BO. The incidence of BO was 4.8%, as the diagnosis was established in 25 patients (4 children). Median time between HSCT and diagnosis of BO was 356 (84-1823) days. Eight patients (32%) had radiologic changes consistent with BO. Forced expiratory volume for 1 second (FEV_1) and forced expiratory flow at 50% (FEF_{50}) and 75% (FEF_{75}) of forced vital capacity (FVC) produced median values that were 49%, 25%, and 18% of the reference values at the time of BO diagnosis. FEF_{75} was reduced before BO diagnosis in 7 patients (28%). In a multivariate risk factor analysis, chronic graft-versus-host disease (cGVHD) was found to be associated with BO ($P < .001$), whereas donor lymphocyte infusion (DLI) diminished the risk ($P = .02$). For 10 patients with late BO (>1 year after HSCT), 80% survived 5 years after diagnosis, compared to 38% survival in 15 patients with early-onset BO ($P = .06$). We conclude that lung function tests with a persistent decrease in FEV_1 were more important than radiographic methods to recognize and monitor BO, that FEF_{75} may serve as an early warning of BO, and that late-onset BO appears to be associated with better outcome. Chronic GVHD was confirmed as a risk factor, and administration of DLI may diminish the risk.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) has become a widely accepted treatment for malignancies and lymphohematopoietic failure syndromes. Despite the advances in histocompatibility matching, new and better treatments for infectious complications, and better immunosuppressive drug treatments, pulmonary complications have continued to be common and often lethal [1-4]. Bronchiolitis obliterans (BO) is a serious, noninfectious pulmonary disorder associated with a poor prognosis [1-3,5]. The underlying pathogenic mechanisms are poorly understood, and the etiology remains obscure (1,3). The most important factor associated with BO has been shown to be the presence of chronic graft-versus-host disease (cGVHD) [6-9]. BO is histologically characterized by obliteration of the lumen of the respiratory bronchioles by organizing granulation tissue, infiltration of mononuclear cells, or fibrosis, and clinically by persistent, progressive obstruction of air flow [1,3,5,10]. In this retrospective single-center study, we determined the incidence of BO, risk factors, and outcome in HSCT recipients who developed this complication, and we evaluated the use of radiology and pulmonary function tests to establish the diagnosis.

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PATIENTS AND METHODS

Patients and Donors

Between January 1995 and December 2003, 527 patients underwent allogeneic HSCT at Karolinska University Hospital, Huddinge. Seventy-seven patients died within 120 days of HSCT, and 102 patients

had insufficient follow-up data because they lived in other countries or because of the lack of lung function tests. In the remaining 330 patients, a total of 1177 lung function tests were performed. For these 330 patients, all spirometries were carefully studied and re-evaluated by an experienced physiologist and a lung specialist. Patients with spirometries showing no or minimal air flow obstruction with normal or nearly normal forced expiratory volume for 1 second (FEV_1), forced expiratory flow at 50% (FEF_{50}), and 75% (FEF_{75}) values were regarded as non-BO cases. Patients with mild, moderate, or severe obstruction of air flow (FEV_1 66%-80%, 51%-65%, or ≤50%) [1,11] were investigated concerning clinical findings and radiographic, pathologic, and laboratory data. Cases that did not fulfill the National Institutes of Health (NIH) criteria for BO [12] were then screened as non-BO cases.

There were 295 male patients and 232 female patients, with a median age of 34 years (range: <1 to 77). Most patients had malignancies (n = 471), mainly acute leukemia (n = 242) or chronic leukemia (n = 110). Donors were an HLA-identical sibling or related individual (n = 227), an HLA-A, -B, and -DRB1 matched unrelated donor (MUD) (n = 246), or a mismatched related/unrelated donor (n = 54). Nonmalignant disorders included severe aplastic anemia (SAA) (n = 23), Fanconi's anemia (FA) (n = 5), paroxysmal nocturnal hemoglobinuria (PNH) (n = 2), and various inherited metabolic disorders. Polymerase chain reaction (PCR) sequence-specific primer (SSP) high-resolution typing was used for both HLA class I and II antigens [13].

The study was approved by the ethics committee of Karolinska Institutet (DNR 425/97). Characteristics of donors and of patients with or without BO are given in Table 1.

Conditioning and GVHD Prophylaxis

Myeloablative conditioning was administered to 417 patients and consisted of cyclophosphamide (Cy) at 120 mg/kg in combination with 7.5-10 Gy single-dose total-body irradiation (TBI) (n = 172) or fractionated (fTBI) 4 × 3 Gy (n = 94) (TBI-based) or busulfan (Bu) at 16 mg/kg (n = 136). Ten patients with SAA received Cy at 200 mg/kg, and 5 with FA

Table 1. Characteristics of Patients Who Underwent Allogeneic Hematopoietic Stem Cell Transplantation in the Period 1995 to 2003, According to Whether or Not They Developed Bronchiolitis Obliterans (BO)

	All Patients	BO	No BO
Diagnosis	n = 527	n = 25	n = 502
Nonmalignant disorder	56	1 (4%)	55 (11%)
Acute leukemia	242	12 (48%)	230 (46%)
Chronic leukemia	110	8 (32%)	102 (20%)
Other malignancy	119	4 (16%)	115 (23%)
Disease stage (early/late)	259/229	15/10	244/219
Sex (M/F)	295/232	14/11	281/221
Age	34 (<1-77)	33 (6–64)	34 (<1-77)
Donor			
HLA-identical related	227	12 (48%)	215 (43%)
MUD	246	11 (44%)	235 (47%)
Mismatched	54	2 (8%)	52 (10%)
Donor sex (M/F)	305/220	12/13	293/207
Donor age	37 (0-71)	37 (19-66)	37 (0-71)
Stem cell source (BM/PBSCs)	280/247	10/15	270/232
NC dose ($\times 10^8$/kg)	4.6 (0.03-80)	8.5 (0.7-25.6)	4.6 (0.03-80)
Female donor to male recipient	101 (19%)	6 (24%)	95 (19%)
G-CSF after HSCT	341 (65%)	20 (80%)	321 (64%)
Previous HSCT (auto/allo)	42 (8%)	3 (12%)	39 (8%)
Conditioning			
MAC	417	23 (92%)	394 (78%)
TBI-based	266	13 (52%)	253 (50%)
Non-TBI	151	10 (40%)	141 (28%)
RIC	110	2 (8%)	108 (22%)
ATG	349 (66%)	14 (56%)	335 (67%)
GVHD prophylaxis			
CsA + MTX	430 (82%)	23 (92%)	407 (81%)
CsA + MMF	45	0	45
Other	52	2 (8%)	50
DLI treatment	126 (24%)	2 (8%)	124 (25%)*
Acute GVHD II-IV	155 (29%)	7 (28%)	148 (30%)
Chronic GVHD	194 (37%)	22 (88%)	172 (34%) **
Follow-up (years)	7.0 (3.2-12.1)	7.6 (3.2-11.0)	7.0 (3.2-12.1)

BM indicates bone marrow; PBSCs, peripheral blood stem cells; NC dose nucleated cell dose; G-CSF, granulocyte-colony stimulating factor; SCT, stem cell transplantation; MAC, myeloablative conditioning; TBI, total-body irradiation; RIC, reduced-intensity conditioning; ATG, antithymocyte globulin; GVHD, graft-versus-host disease; CsA, cyclosporine A; MTX, methotrexate; MMF, mycophenolate mofetil; DLI, donor lymphocyte infusion.
Disease stage: early, CR1/CP1 (first complete remission/first chronic phase), or nonmalignant disorder; late, beyond CR1/CP1; MUD, HLA-A-, -B-, and -DRB1 matched unrelated donor.
*$P = .05$, ** $P < .001$.