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A Novel GVHD-Prophylaxis with Low-Dose Alemtuzumab in Allogeneic Sibling or Unrelated Donor Hematopoetic Cell Transplantation: The Feasibility of Deescalation

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Prophylaxis of acute graft-versus-host disease (aGVHD), while maintaining the graft-versus-leukemia (GVL)/lymphoma effect and preventing severe infectious diseases, remains the main challenge in allogeneic hematopoetic cell transplantation (allo-HCT). To evaluate this, we examined the feasibility of deescalating the dose of alemtuzumab (MabCampath™) in combination with cyclosporine (CsA) as the sole GVHD-prophylaxis in patients after fludarabine (Flu)-based reduced-intensity conditioning (RIC) in an observational cohort study. We included 127 consecutive patients (median age 63 years) with an unrelated (UD; n=69) or related donor (SIB; n=58) after their first transplantation, mostly presenting with advanced disease. The first 30 patients received 20 mg/day on day −2 and −1 (40 mg), the following 48 patients 10 mg/day on day −2 and −1 (20 mg), and the last 49 patients 10 mg on day − 1 (10 mg) alemtuzumab intravenous (i.v.) prior to transplant. We observed no statistical differences comparing the 40 mg, 20 mg, or 10 mg dose groups, in terms of cumulative incidences of aGVHD grade III-IV 7% (confidence interval [CI] 95%; 1-51), 12% (1-40), 6% (1-40), extensive chronic GVHD (cGVHD) 24.4% (3.3-55.8), 17% (2.5-42), and 14.2% (1.5-41.5) and of aGVHD grade II-IV 7 % (0-51.5), 29% (11.9-49.1), 21% (15.3-43.1), respectively. The difference between the 20-mg and 40-mg groups was significant for aGVHD grade II-IV($P < .05$). In conclusion, we demonstrate the feasibility of reducing the dose of alemtuzumab as GVHD-prophylaxis to 10 mg absolute in combination with CsA only for UD transplantation in particular.

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INTRODUCTION

To reduce the incidence and severity of acute graft-versus-host disease (aGVHD), especially in volunteer unrelated donor transplantation (UD), polyclonal antibodies like antithymocyte globulin (ATG) have been used in combination with standard cyclosporine/methotrexate (CsA/MTX) prophylaxis [1]. A group of monoclonal antibodies (mAbs) against CD52 (Campath-1) were introduced [2] to deplete recipient and donor T cells, provide engraftment, and prevent severe aGVHD. The anti-CD52 antibody was initially used for in vitro T cell depletion by exposing stem cell products to the rat Campath-1 G, a procedure called "Campath in the bag" [3]. Campath-1H (alemtuzumab) is a humanized IgG 1 mAb that recognizes the CD52 antigen on human lymphocytes, natural killer (NK) cells, monocytes/macrophages, dendritic cells, and eosinophils, but not on hematopoetic stem cells (HSCs) [4,5]. Campath-1H has been studied in vitro [6] and used in vivo as part of conditioning regimens since 1997 [7].

Initially, the total dose of alemtuzumab was 100 mg total dose given i.v. over 5 days prior to transplantation [2,7]. Although panlymphocyte depletion resulted in significantly less GVHD, there was increased incidence of severe viral and opportunistic infections, graft failure, and relapse. To prevent these complications, 2 groups reduced the alemtuzumab dose as part of the conditioning regimen to 50 mg total

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dose in sibling and UD transplantation [8,9] in addition to using calcineurin inhibitors and MTX as GVHD prophylaxis.

In an effort to reduce infectious complications and maintain a significant graft- versus-malignancy effect, we aimed at further reducing the total dose of alemtuzumab dose and substituting MTX and mycophenolatmofetil (MMF), because of their side effects as part of the GVHD prophylaxis in our reduced-intensity conditioning (RIC) protocols [10-12]. The observational design was to initially use alemtuzumab 40 mg total dose and deescalate to 20 mg total if aGVHD and mortality rates did not increase in 70 patients compared to our standard GVHD prophylaxis used before, consisting of CsA/MMF or CsA/MTX. Further alemtuzumab tapering (10 mg total) was dependent on the noninferiority of 20 mg to 40 mg after interim analysis of significant numbers of patients treated. Therefore, in 2002, we incorporated lower doses of alemtuzumab (total 40 mg) as part of our GVHD prophylaxis in combination with CsA into our internal review board (IRB) and ethics committee-approved RIC protocol designed for relapsed patients undergoing second allogeneic transplantation [10], and since 2003, included it in our primary RIC-protocol study protocol [11,12]. As we did not observe higher incidences of aGVHD and morbidity, we further amended the protocol to deescalate the alemtuzumab dose to 20 mg total, and later, a 10-mg total dose.

Here we report data from our observational study with 3 consecutive patient cohorts after their first transplantation receiving the i.v. administration of 3 doses of alemtuzumab (40 mg, 20 mg, and 10 mg) in combination with CsA as GVHD prophylaxis.

Our experience in 127 consecutive patients with hematologic malignancies who underwent UD (n=69) or sibling donor (n=58) transplantation show similar results for aGVHD and extensive chronic GVHD (cGVHD).

PATIENTS AND METHODS

Patient Characteristics

Patient characteristics are listed in Table 1. The 127 patients received their first transplantation for de novo acute myelogenous leukemia (AML, n=35), therapy-related or secondary AML or myelodysplastic syndrome (MDS0, refractory anemia (RA), refractory anemia with excess blasts (RAEB) 2, refractory anemia with excess blasts in transformation (RAEB-T), chronic myelomonocytic leukemia (CMMoL) (n=50), acute lymphoblastic leukemia (ALL; n=7), non-Hodgkin lymphoma (NHL)/Hodgkin lymphoma (HL)/multiple myeloma (MM)/chronic lymphocytic leukemia (CLL) (n=27), and chronic myelogenous leukemia (CML)/other myeloproliferative syndromes (MPS) (n=8). The 53 female and 74 male patients had a median age of 63 years (24-76 years). At transplantation, 30 patients were untreated, 18 patients were in first complete remission or first chronic phase (CR1/CP1), and all other patients (n=79) had advanced disease (CR>1, >CP1, persistent induction failure, relapse ≥1, progressive disease, partial remission, stable disease). One hundred three of the 127 patients (81%) were at risk at transplantation for cytomegalovirus (CMV) infection/disease because of positive pretransplant CMV serology in the patient and/or donor.

Table 1. Patients, Transplantation, and Donor Characteristics

Alemtuzumab dose	40 mg (n=30)	20 mg (n=48)	10 mg (n=49)
Time period of HCT	2003-2005	2005-2006	2006-2007
Age in median	61.4 y (39-71)	64.8 y (30-75)	63.7 y (24-76)
Diagnosis	n (%)	n (%)	n (%)
De novo AML	6 (20)	9 (19)	20 (41)
t,s,ts AML/MDS,MDS	5 (17)	22 (46)	23 (47)
NHL, HL, MM, CLL	15 (50)	10 (21)	2 (4)
ALL	0	5 (10)	2 (4)
CML/MPS	4 (13)	2 (4)	2 (4)
Remission at HCT			
CR1/CP1	5 (17)	8 (17)	5 (10)
Untreated	5 (17)	15 (31)	10 (20)
advanced			
(PIF, REL, PROG, >CR1)	20 (66)	25 (52)	34 (70)
Conditioning regimens			
Flu/B/Mel	29 (97)	44 (92)	45 (92)
Flu/TT	1 (3)		
Flu/B/TT	4 (8)	4 (8)	
Donor characteristics			
Male: female	15:15	32:16	27:22
Sibling:UD	24:6	14:34	20:29
BM: PBSC	1:29	2:46	0:49
HLA mismatch >1	1 (3)	2 (4)	0
A, B, C	2 (7)	12 (25)	8 (16)
DRB1, DQB1	1 (3)	2 (4)	1 (3)
CMV serology			
D^+/P^-	4 (13)	4 (8)	8 (16)
D^-/P^+	10 (34)	10 (21)	11 (22)
D^+/P^+	12 (40)	26 (54)	18 (37)
D^-/P^-	4 (13)	8 (16)	12 (25)
G-CSF post-TX	8 (27)	0	0

y indicates years; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; tAML, therapy-associated AML; sAML, secondary AML; tsAML, therapy-associated secondary AML; MDS, myelodysplastic syndrome; MPS, myeloproliferative syndrome; NHL non-Hodgkin lymphoma; CLL, chronic lymphocytic lymphoma; MM, multiple myeloma; HCT, hematopoetic cell transplantation; CR, complete remission; CP, chronic phase; REL, relapse; PIF, persistant induction failure; other, chronic phase, accelerated phase, blast crisis, progression, partial remission, stable disease; TX, transplantation; allo, allogen; auto, autologous; UD, unrelated donor; CMV, cytomegalovirus; D, donor; P, patient; G-CSF, granulocyte colony-stimulating factor; Flu, fludarabine; B, carmustin; Mel, melphalan; TT, thiotepa.

Conditioning Regimen, GVHD Prophylaxis, and Stem Cell Source

All patients received fludarabine (Flu)-based RIC regimens. Inclusion criteria have been published elsewhere [10-12]. One hundred eighteen patients received Flu (Schering, Berlin, Germany) 30 mg/m^2/day given from day −9 to day −5 (since July 2005: Flu 30 mg/m^2 ×4 days from day −8 to day −5), carmustine (Bristol Myers Squibb, Munich, Germany) 200 mg/m^2/day