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Ex Vivo CD34+–Selected T Cell–Depleted Peripheral Blood Stem Cell Grafts for Allogeneic Hematopoietic Stem Cell Transplantation in Acute Leukemia and Myelodysplastic Syndrome Is Associated with Low Incidence of Acute and Chronic Graft-versus-Host Disease and High Treatment Response

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A B S T R A C T

Ex vivo CD34+–selected T cell depletion (TCD) has been developed as a strategy to reduce the incidence of graft-versus-host disease (GVHD) after allogeneic (allo) hematopoietic stem cell transplantation (HSCT). Clinical characteristics, treatment responses, and outcomes of patients developing acute (aGVHD) and chronic GVHD (cGVHD) after TCD allo-HSCT have not been well established. We evaluated 241 consecutive patients (median age, 57 years) with acute leukemia (n = 191, 79%) or myelodysplastic syndrome (MDS) (n = 50, 21%) undergoing CD34+–selected TCD allo-HSCT without post-HCST immunosuppression in a single institution. Cumulative incidences of grades II-IV and III-IV aGVHD at 180 days were 16% (95% confidence interval [CI], 12 to 21) and 5% (95% CI, 3 to 9), respectively. The skin was the most frequent organ involved, followed by the gastrointestinal tract. Patients were treated with topical corticosteroids, poorly absorbed corticosteroids (budesonide), and/or systemic corticosteroids. The overall day 28 treatment response was high at 82%. The cumulative incidence of any cGVHD at 3 years was 5% (95% CI, 3 to 9), with a median time of onset of 256 days (range, 95 to 1645). The 3-year transplant-related mortality, relapse, overall survival, and disease-free survival were 24% (95% CI, 18 to 30), 22% (95% CI, 17 to 27), 57% (95% CI, 50 to 64), and 54% (95% CI, 47 to 61), respectively. The 1-year and 3-year probabilities of cGVHD-free/relapse-free survival were 65% (95% CI, 59 to 71) and 52% (95% CI, 45 to 59), respectively. Our findings support the use of ex vivo CD34+–selected TCD allograft as a calcineurin inhibitor–free intervention for the prevention of GVHD in patients with acute leukemia and MDS.

INTRODUCTION

Graft-versus-host disease (GVHD) contributes significantly to transplant-related morbidity and mortality (TRM) after allogeneic (allo) hematopoietic stem cell transplantation (HSCT) [1]. Investigators have, therefore, addressed this issue by improving selection of patients at lower risk for GVHD [2], using biomarkers to facilitate early diagnosis and

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treatment [3-5] and proving efficacy of innovative prophylactic [6-10] and therapeutic strategies [11,12]. Depletion of T cells in the graft through ex vivo CD34+ cell–positive selection represents one of the approaches to prevent GVHD. Although investigators have documented the clinical characteristics of GVHD, therapeutic approaches, and outcomes of patients developing acute GVHD (aGVHD) and chronic GVHD (cGVHD) after unmodified grafts for allo-HSCT [13-17], there are no comprehensive studies specifically addressing these issues in the CD34+ hematopoietic progenitor cells–selected graft setting [18]. This type of graft manipulation has unique features, which should lead to distinct incidences, clinical presentations, and outcomes of patients with and without aGVHD or cGVHD. We, therefore, investigated the clinical characteristics of aGVHD and cGVHD and the risk factors associated with aGVHD in a homogeneous cohort of patients diagnosed with acute leukemia and myelodysplastic syndrome (MDS) undergoing ex vivo CD34+–selected allo-HSCT.

METHODS

Patient and Graft Characteristics

This analysis included patients who underwent allo-HSCT at Memorial Sloan Kettering Cancer Center (MSKCC) between January 1, 2008 and May 31, 2014. Patients eligible for this analysis included all consecutive adult recipients of first allografts who underwent transplantation for the treatment of acute myeloid leukemia, acute lymphoblastic leukemia, or MDS. Eligibility for this study required that acute leukemia patients be in complete remission and MDS patients had to have ≤ 5% blasts in pretransplantation bone marrows. Disease risk was assessed using the disease risk index for allo-HSCT [19]. Patients with donor-recipient HLA-match < 7/8 were excluded from the analysis. Fourteen patients enrolled in the CMX001 clinical trial for the management of cytomegalovirus were also excluded because this drug is associated with a higher incidence of gastrointestinal (GI) aGVHD [20]. All patients provided written informed consent for transplantation according to the principles of the Declaration of Helsinki, and transplantation outcome analysis was approved by the MSKCC institutional review and privacy board. Patients included in this analysis underwent transplantation on trials NCT01746849, NCT01596257, NCT01119066, NCT00629798, NCT00201240, and NCT00582933, registered at ClinicalTrials.gov.

HLA typing used high-resolution DNA sequence-specific oligonucleotide typing for HLA-A, -B, -C, -DRB1, and -DQ (5 allele level). Donor selection used matching at 10 HLA alleles. For the purpose of this analysis, however, only 8 HLA-allele matching at -A, -B, -C, and -DRB1 was considered. Assessment of comorbidities and calculation of the hematopoietic cell transplantation comorbidity index (HCT-CI) followed standard recommendations [21,22].

All patients received CD34+-selected grafts from granulocyte colony–stimulating factor–mobilized peripheral blood stem cells. CD34+ hematopoietic progenitor cells were selected using the Isolex 300i Magnetic Cell Separator (Baxter, Deerfield, IL), followed by additional T cell rosetting with neuraminidase-treated sheep erythrocytes [23] or using the CliniMACS CD34+ Reagent System (Miltenyi Biotech, Gladbach, Germany) [24]. The Isolex system was only used in allo-HSCT from 2008 to 2010, when it became commercially unavailable. The CD34+-selected T cell depleted (TCD) graft was infused within the first 48 hours after manipulation.

Conditioning Regimens and Supportive Care

Pretransplantation conditioning included either cyclophosphamide (120 mg/kg), thiotepa (10 mg/kg), and hyperfractionated total body irradiation [TBI] (1375 cGy), or intravenous busulfan (9.6 mg/kg), melphalan (140 mg/m^2), and fludarabine (125 mg/m^2). A few patients enrolled in specific protocols received other conditioning regimens (Table 1). Granulocyte colony–stimulating factor (5 mcg/kg/day) was given to all patients from day 7 until absolute neutrophil count recovery of > 2.0×10^9/L.

All patients were hospitalized in high-efficiency particulate air–filtered rooms and received similar supportive care. Management of early toxicities, engraftment, and infections was performed according to standard clinical practice, as previously described [25-27].

GVHD Prophylaxis, Diagnosis, and Treatment

All patients received antithymocyte globulin (ATG) before HSCT for the prevention of allograft rejection. The dose of ATG was 2.5 mg/kg/day on days -3 and -2 except in 20 7/8 HLA–matched and 3 HLA-DQ mismatched recipients who received 1 additional day of ATG treatment from days -3 to -1. Patients did not receive calcineurin inhibitor or any other immunosuppressive prophylaxis after HSCT.

aGVHD and cGVHD were diagnosed clinically with histological confirmation as required when clinically appropriate. Treatment of aGVHD followed institutional and national guidelines [28]. Patients received either topical corticosteroids, poorly absorbed corticosteroids, or systemic corticosteroids according to organ involvement and clinical GVHD severity at the time of diagnosis. Calcineurin inhibitor was used frequently in patients with visceral aGVHD involvement who required systemic corticosteroids therapy.

Study Definitions

The International Bone Marrow Transplant Registry classification guided the aGVHD grading, except grades A to D were labeled grades I to IV. GVHD

Table 1
Patient and Graft Characteristics

Characteristic	Value
Patient characteristics	
No. of patients	241
Age, median (range), yr	57 (20-73)
Male gender	134 (56)
Donor/recipient gender	
Female to male	46 (19)
Other	195 (81)
Donor*	
MRD	90 (37)
MMRD	3 (1)
MUD	100 (42)
MMUD	48 (20)
Patient CMV serostatus	
Seronegative	105 (44)
Seropositive or equivocal	136 (56)
Diagnosis	
Acute myeloid leukemia	162 (67)
Acute lymphoblastic leukemia	29 (12)
MDS	50 (21)
Disease risk	
Low	5 (2)
Intermediate	207 (81)
High	43 (17)
Disease status for acute leukemia†	
CR1	155 (81)
CR2-3	36 (19)
HCT-CI, n (%)	
0	41 (17)
1-2	88 (37)
≥3	112 (46)
Conditioning regimen	
Bu/Mel/Flu	147 (61)
Cy/Thio/TBI (1375cGy)	77 (32)
Clo/Mel/Thio	11 (5)
Flu/Thio/TBI (1375cGy)	6 (2)
Year of HSCT	
2008-2010	97 (40)
2011-2014	144 (60)
Graft characteristics	
Infused cell dose, median (range)	
TNC × 10^8/kg	7.9 (1.6-28.6)
CD34+ × 10^6/kg	7.7 (1.5-28.4)
CD3+ × 10^3/kg	2.3 (.3-37)
Donor-recipient HLA match‡	
8/8	200 (83)
7/8	41 (17)
CD34+ selection method	
Isolex	70 (29)
CliniMACS	171 (71)

Data presented are n (%) unless otherwise indicated.
MRD indicates matched related donor; MMRD, mismatched related donor; MUD, matched unrelated donor; MMUD, mismatched related donor; CR, complete remission; Bu, busulfan, Mel, melphalan, Flu, fludarabine; Cy, cyclophosphamide; Thio, thiotepa; Clo, clofarabine; Mel, melphalan; TNC indicates total nucleated cells.
* At 8 allele level (-A,-B,-C, and -DRB1).
† Percentage calculated based on acute leukemia patients only.
‡ Considering -A, -B, -C, and -DRB1 HLA loci.