ASBMT
American Society for Blood and Marrow Transplantation

ATG Prevents Severe Acute Graft-versus-Host Disease in Mismatched Unrelated Donor Hematopoietic Cell Transplantation

Joseph Pidala,[1,2] Marcie Tomblyn,[1,2] Taiga Nishihori,[1,2] Ernesto Ayala,[1,2] Teresa Field,[1,2] Hugo Fernandez,[1,2] Lia Perez,[1,2] Fred Locke,[1,2] Melissa Alsina,[1,2] Jose Leonel Ochoa,[1,2] Janelle Perkins,[1,2] Cheryl Tate,[1] Jamie Shapiro,[1] Michelle Conwell,[1] Ryan Bookout,[1] Claudio Anasetti[1,2]

Severe acute graft-versus-host disease (aGVHD) remains a major source of morbidity and mortality following mismatched unrelated donor hematopoietic cell transplantation (HCT). Through a retrospective analysis, we investigated the efficacy of GVHD prophylaxis with rabbit anti-thymocyte globulin (ATG) 7.5 mg/kg (1 mg/kg given on day −3, then 3.25 mg/kg/day on days −2 and −1 before stem cell infusion) followed by standard tacrolimus plus methotrexate in a consecutive series of 45 HLA partially matched unrelated donor HCT recipients. The cumulative incidence of grade III-IV aGVHD was 11% by 100 days (95% confidence interval [CI] 5%-25%). Moderate to severe chronic GVHD (per NIH consensus criteria) was 19% (95% CI 10%-36%) at 1 year, and 28% (95% CI 16%-48%) at 2 years. With a median follow-up time for surviving patients of 12 months (range: 5-39 months), overall survival was 55% (95% CI 39%-71%) at 1 year, and 45% (95% CI 27%-63%) at 2 years. Nonrelapse mortality was 11% (95% CI 5%-25%) by 100 days post-HCT, 26% (95% CI 16%-44%) by 1 year, and 30% (95% CI 18%-50%) by 2 years. The cumulative incidence of primary disease relapse was 23% (95% CI 13%-41%) at 1 year, and 33% (95% CI 20%-56%) by 2 years after HCT. Cytomegalovirus (CMV) infection or reactivation varied according to recipient and donor CMV serostatus. Epstein-Barr Virus (EBV) reactivation occurred in 54% (95% CI 40%-71%) of patients. Preemptive rituximab therapy was administered for EBV reactivation, however, posttransplant lymphoproliferative disorder was diagnosed in 5 (11%) cases, and was fatal in 1. A regimen of ATG 7.5 mg/kg total ending on day −1 effectively decreased the occurrence of grade III-IV aGVHD and severe chronic GVHD.

Biol Blood Marrow Transplant 17: 1237-1244 (2011)

KEY WORDS: Acute graft-versus-host disease, Antithymocyte globulin, Mismatched unrelated donor transplantation

INTRODUCTION

Acute and chronic graft-versus-host disease (aGVHD, cGVHD) remain significant sources of morbidity and mortality following allogeneic donor hematopoietic cell transplantation (HCT). As donor alloreactive T cells are principal mediators of the syndrome, in vivo T cell depletion by antilymphocyte antibodies have been studied in the prevention [1,2], pre-emptive therapy [3,4], and treatment of established GVHD following HCT [5-10].

The efficacy of anti-thymocyte globulin (ATG) in the prevention of both aGVHD and cGVHD is supported by evidence including retrospective comparative data [11-15] as well as randomized and nonrandomized prospective clinical trials [16-28]. Studies have demonstrated reduction in aGVHD, and long-term follow up has demonstrated significantly lower cGVHD, lung dysfunction, and late nonrelapse mortality (NRM) in those treated with ATG [29,30]. Alongside the beneficial reduction in GVHD, the use of ATG delays immune reconstitution [31-34] and confers an increased risk of Ebstein-Barr virus (EBV) reactivation and EBV-associated posttransplant lymphoproliferative disease (PTLD) [35,36]. Risk of PTLD increases with age, T cell depletion, ATG

From the [1]Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, Florida; and [2]Oncologic Sciences, University of South Florida, Tampa, Florida.

Financial disclosure: See Acknowledgments on page 1243.

Correspondence and reprint requests: Joseph Pidala, MD, MS, Blood and Marrow Transplantation, Moffitt Cancer Center, University of South Florida, Tampa, FL 33612 (e-mail: joseph.pidala@moffitt.org).

Received November 26, 2010; accepted December 29, 2010

1083-8791/$36.00
doi:10.1016/j.bbmt.2010.12.705

use, and unrelated or HLA-mismatched grafts [34]. Posttransplantation monitoring of EBV viral load and preemptive rituximab therapy is effective in controlling EBV and preventing PTLD in the majority of cases [37-40].

Diverse approaches to the delivery of antilymphocyte antibodies have been pursued to date, including the following: rabbit ATG (Thymoglobulin) 4.5 mg/kg total, divided over 3 days concluding on day 0 [12]; Thymoglobulin 7.5 mg/kg total, divided on days −4 and −3, or Thymoglobulin 15 mg/kg total, divided from days −5 to −2 [16]; and ATG-Fresenius (ATG-F; Fresenius Biotech, Graefelfing, Germany) total dose ranging from 30 to 90 mg/kg, ending on day −1 [11,19,41]. Comparative data suggest that ATG potency varies among formulations, increases with dose and with shorter time interval to HCT [16,41-43]. Here, we report the safety and efficacy of Thymoglobulin 7.5 mg/kg total, administered over 3 days ending on day −1, for the prevention of aGVHD in mismatched unrelated donor HCT.

METHODS

Patient Characteristics

Adult patients who received ATG for GVHD prophylaxis before HLA mismatched, unrelated donor HCT were the subjects of a retrospective study approved by the University of South Florida institutional review board. Consecutive patients between September 2006 and March 2010 were identified by review of existing database records. Inclusion criteria were the use of ATG as GVHD prevention, and a transplant from an HLA mismatched unrelated donor. Recipient-donor pairs with sole mismatch at HLA-DQ, or complete allelic matching at loci A, B, C, and DR were excluded. Additionally, recipients of umbilical cord blood stem cells were excluded from this analysis. The principal aim of the study was to estimate the cumulative incidence of grade III-IV aGVHD.

Baseline characteristics included the following: date of HCT; stem cell product infusion time; recipient and donor HLA typing; recipient and donor age, gender, and cytomegalovirus (CMV) serostatus; disease condition and remission status at time of HCT; conditioning regimen; aGVHD prophylaxis agents; and ATG utilization (start date and time, schedule of delivery, total dose delivered, stop date, and time).

Standardized data abstraction was performed. Neutrophil engraftment was defined by the first of 3 successive days with an absolute neutrophil count of >500/μL. Platelet engraftment was defined by the first of 3 successive days with a nontransfused platelet count of >20,000/μL. Primary graft failure was defined as failure to achieve a neutrophil count of ≥500/μL in patients who survived ≥28 days following transplantation and who have not undergone a second transplant procedure. Secondary graft failure was defined as a decline of neutrophils to <500/μL after having engrafted that is unresponsive to growth factors. Acute GVHD was scored per modified Glucksberg criteria [44]. Chronic GVHD was scored per the proposed NIH consensus criteria [45]. Chimerism was assessed by capillary electrophoresis of single tandem repeats on peripheral blood sorted CD3- and CD33-positive cells and bone marrow cells at days 30, 90, 180, and 360. Absolute lymphocyte counts, and lymphocyte subsets were quantified at 3, 6, and 12 months following HCT. Data collected included CMV reactivation onset date and serum copy number, peak date and copy number, number of discrete episodes of reactivation, the occurrence and site of CMV disease, and CMV therapy delivered. Data also included the date and log copy number of EBV reactivation, peak date, and copy number, number of doses of rituximab delivered, and the occurrence of PTLD. Data were also gathered on the occurrence of adenovirus, HHV-6, and BK virus following HCT. The occurrence of bacterial and invasive fungal infections was also captured.

Conditioning Therapy and ATG Regimen

The conditioning regimen in 41 of the 45 cases consisted of fludarabine, 40 mg/m^2 infused over 30 minutes on days −6 to −3, followed by intravenous busulfan, 130 to 145 mg/m^2 over 4 hours daily on the same days. Busulfan PK-samples were obtained on day −6 and analyzed by mass spectrometry; on days −4 and-3. The busulfan dose was adjusted to target an average area under the curve (AUC) of 5300 (±10%) μMol*min (n = 36) or 3500 (±10%) μMol*min (n = 3) for each of the 4 days; the reduced busulfan target AUC was selected according to transplant physician discretion in these 3 cases because of patient age at transplant (range: 62-67 years of age). Two patients were enrolled on a prospective trial examining dose escalation of i.v. pharmacokinetic- targeted busulfan and fludarabine with a target average AUC of 7500 μMol*min. Three patients (multiple myeloma, n = 2, acute myelogenous leukemia, n = 1) received fludarabine 40 mg/m^2 on days −5 through −2 with melphalan 70 mg/m^2 on day −2. Finally, 1 patient with aplastic anemia was conditioned with fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 on days −5 through −2, and 200 cGy total-body irradiation (TBI) on day 0.

The ATG regimen provided a total of 7.5 mg/kg rabbit ATG, administered as 1 mg/kg on day −3 (over ≥6 hours), then 3.25 mg/kg/day on days −2 and −1 (over ≥4 hours) prior to the stem cell infusion. The dose of ATG was based on actual body weight; however, if actual body weight was ≥30% ideal body