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Unrelated Donor Transplantation for Acute Myelogenous Leukemia in First Remission

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We retrospectively analyzed the outcomes of all acute myelogenous leukemia (AML) patients in first remission (n = 44; median age = 48 years; high-risk cytogenetics = 59%) who received unrelated donor hematopoietic cell transplantation (HCT) with myeloablative conditioning regimen of i.v. busulfan, fludarabine, and antithymocyte globulin (ATG) between January 2002 and November 2009 at our institution. Donor-recipient pairs were matched by high-resolution HLA-A, -B, -C, -DRB1, and -DQB1 typing (10/10 matches, n = 41; 9/10 matches, n = 3). With a median follow-up of 34 months, actuarial 3-year event-free survival (EFS) and overall survival (OS) is 70% and 78%, respectively. The 3-year EFS and OS in patients with and without poor risk cytogenetics is similar (63% versus 82%, $P = 0.43$ and 78% versus 82%, $P = .89$, respectively). The 3-year EFS and OS is also similar in patients above age 55 year versus patients age 55 year or younger (80% versus 67%, $P = .47$ and 80% versus 78%, $P = .81$, respectively). The 100-day and 3-year cumulative incidence of transplant-related mortality is 5% and 15%, respectively. Six patients have relapsed, and 3 of them are alive and in remission after salvage therapy, with a median follow-up of 23 months. These results indicate that the majority of AML patients eligible for this treatment can achieve long-term disease control.

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INTRODUCTION

Approximately 70% of adult patients with acute myelogenous leukemia (AML) achieve first complete remission (CR1) with induction chemotherapy, but the great majority relapse without consolidation therapy [1]. Allogeneic hematopoietic stem cell transplantation (HSCT) is generally recommended for patients with poor-risk cytogenetics and often considered also for patients with intermediate-risk AML in CR1 [2]. HSCT-related toxicity, primarily regimen-associated adverse events and graft-versus-host disease (GVHD), has limited its more widespread application [3]. However, newer conditioning regimens have contributed to a dramatic reduction in the incidence of serious transplant-related adverse events and transplant-related mortality (TRM) in the last 10 years [4]. For instance, myeloablative doses of intravenous (i.v.) Busulfan (Bu) in combination with the nucleoside analogue fludarabine (Flu) are associated with low toxicity rates, and possibly lower GVHD incidence [4-8].

Most patients will not have a human histocompatibility antigen (HLA)-compatible donor in the family, and therefore an unrelated donor (UD) transplant will be considered. Outcomes after UD bone marrow (BM) or peripheral blood (PB) HSCT have also improved significantly over the last decade, a result of multiple developments in the field, first and foremost better HLA typing and donor-recipient matching.

We hypothesized that the use of this reduced-toxicity regimen, in combination with improved, high-resolution HLA = typed donor-recipient pairs would lead to improved outcomes comparable to matched-related donor allogeneic HSCT in patients with AML transplanted in CR1 [9,10]. Here, we present our experience, demonstrating that our data support the use of this conditioning regimen as described here.

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METHODS

Patients

Eligible for this analysis were all AML patients in CR1 receiving UD HSCT, consecutively enrolled in 2 prospective clinical trials evaluating the preparative regimen of busulfan and fludarabine (described below). Primary end point of both trials was time to progression and overall survival (OS). One patient who met the criteria for this analysis was treated off protocol because of a low left ventricular ejection fraction.

Patients met general eligibility criteria to undergo myeloablative allogeneic HSCT (age ≤65 years and adequate organ function). Disease-specific criteria included absence of favorable risk cytogenetics (t[8;21], inv 16, t[15;17]) [11], or the requirement of more than 1 cycle of induction chemotherapy to achieve CR1 [12,13]. Fourteen patients have been previously reported [6,8]. All patients signed informed consent, and were treated between January 2002 and November 2009. Both prospective clinical trials and this analysis were approved by the institutional review board at M.D. Anderson Cancer Center.

Treatment and GVHD Prophylaxis

Fludarabine (Berlex Laboratories, Wayne, NJ) 40 mg/m^2/day (days −6 to −3) was administered over 60 minutes, each dose immediately followed by busulfan (Otsuka Pharmaceuticals, Edison, NJ), 130 mg/m^2/day or pharmacokinetically (PK−) targeted at an AUC of 6000 μMol-min ±10% (days −6 to −3), administered over 3 hours. All patients received either rabbit antithymocyte globulin (ATG) (n = 39) (0.5 mg/kg on day −3, 1.5 mg/kg on day −2, and 2 mg/kg on day −1) or equine ATG (n = 5) (20 mg/kg/day on days −3 to −1). All supportive care measures were previously described [6].

GVHD prophylaxis consisted of tacrolimus (Fujisawa Healthcare, Deerfield, IL) administered for 6 to 9 months if no GVHD, and minimethotrexate (5 mg/m^2 on HSCT days 1, 3, 6, and 11) [14]. Pentostatin (Supergen, Dublin, CA) was added to 14 patients under an investigational protocol on HSCT days 8, 15, 22, and 30, at 1 mg/m^2 (n = 4), or 1.5 mg/m^2 (n = 10) [15]. PB or BM cells were obtained through the National Marrow Donor Program (NMDP).

HLA Typing

All donor-recipient pairs were matched using high-resolution allele-level HLA typing for HLA-A, -B, -C, -DRB1, and -DQB1, as previously described [16]. Up to 1 mismatch was allowed.

Analysis of Donor Chimerism and Engraftment

Chimerism analysis was performed on whole blood and on blood mononuclear cells (T and B cells), by polymerase chain reaction (PCR), with primer sets flanking microsatellite repeats as described previously [17]. Neutrophil engraftment was defined to have occurred on the first of 3 consecutive days that the absolute neutrophil count (ANC) exceeded 0.5 × 10^9/L of blood. Platelet engraftment was defined as having occurred on the first of 7 consecutive days that the platelet count exceeded 20 × 10^9/L, independent of platelet transfusions.

Statistical Analysis

Actuarial OS and event-free survival (EFS) curves were estimated using the Kaplan-Meier method [18]. Comparisons between subgroups were performed using the log-rank test. Data were updated as of February 2010. Cumulative incidence rates were calculated using the method of Fine and Gray [19]. All tests were 2-sided and P values of .05 or less were considered statistically significant. Statistical analysis used SAS version 9 (SAS Institute, Cary, NC) and S-Plus 7 (Insightful Inc, Seattle, WA).

RESULTS

Patients

Forty-four patients were transplanted (Table 1). Ten (23%) were older than 55 years and 26 (59%) had poor-risk cytogenetics [11]. Three (7%) patients had 1 donor-recipient HLA-mismatch (9/10) (HLA-A = 1; HLA-B = 1; HLA-C = 1), whereas 33 (75%) patients had 1 or 2 HLA-DPB1 mismatches. Median follow-up is 34 months (range: 4-90).

Engraftment and Chimerism

All patients achieved neutrophil engraftment (Table 1). The median time to engraftment was 12 days (range: 10-19). Two patients developed secondary graft failure associated with severe infections and drug toxicity. Median T lymphocyte and myeloid chimerism at days 30, 100, and 6 months posttransplant was 100% of donor cells at each time point (Table 1).

Transplant-Related Mortality

One hundred-day, and 3-year cumulative incidence of transplant-related mortality (TRM) was 5% (95% confidence interval [CI], 0.89-1) (n = 2) and 15% (95% CI, 0.75-0.97) (n = 7), respectively. TRM causes were secondary graft failure (n = 1), infection (n = 4), acute GVHD (aGVHD) (n = 1), and regimen-related toxicity (n = 1).

Acute GVHD and Chronic GVHD

Grade II-IV aGVHD rate was 23% (n = 10), whereas the cumulative incidence of chronic GVHD