Biol Blood Marrow Transplant 22 (2016) 1816–1822

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Impact of Donor Type on Outcome after Allogeneic Hematopoietic Cell Transplantation for Acute Leukemia

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Article history:
Received 26 May 2016
Accepted 20 July 2016

Keywords:
Haploidentical transplantation
Unrelated donor transplantation
Acute myeloid leukemia
Acute lymphoblastic leukemia
Disease risk index

A B S T R A C T

Allogeneic hematopoietic cell transplantation (alloHCT) is considered the most potent postremission antileukemic therapy in adults with acute leukemia. We analyzed 172 consecutive acute leukemia patients transplanted in complete remission after a T cell–replete alloHCT from either a matched related (MRD, n = 54), unrelated (MUD, n = 67), or haploidentical (haplo, n = 51) donor to look for patient-, disease-, and transplant-related factors associated with post-transplant outcomes. Patients included 123 acute myeloid leukemia patients (first complete remission [CR], n = 94; second CR, n = 28; third CR, n = 1) and 49 acute lymphoblastic leukemia (ALL) patients (first CR, n = 39; second CR, n = 9; third CR, n = 1) with a median age of 50 years (range, 19 to 74). Median follow-up for surviving patients was 38 months. Cumulative incidence of nonrelapse mortality at 1 and 3 years was 6% and 17%, respectively. The estimated rates of 3-year overall survival, disease-free survival, and relapse incidence were 59%, 50%, and 33%, respectively. In multivariate analysis, risk factors for inferior survival included diagnosis of ALL, high risk disease risk index, and use of a female donor for a male recipient. Donor type (MRD, MUD, haplo) had no impact on any transplant outcome. Given the favorable outcomes associated with alloHCT in acute leukemia and lack of effect of donor type, a strong case can be made for transplanting acute leukemia patients in remission as soon as any donor becomes available.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (alloHCT) is an established treatment for patients with acute leukemia and represents the most active form of antileukemic therapy in patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). This fact reflects both the inadequacy of conventional chemotherapy approaches and the increasing understanding that a potent graft-versus-leukemia response may be exploited in these patients [1-3].

At the same time, it is also well established that a significant part of the beneficial effect of alloHCT is offset by an increase in nonrelapse mortality (NRM) that is typically associated with this form of therapy. The major causes of NRM after alloHCT are regimen-related toxicities, graft-versus-host disease (GVHD), and opportunistic infections. Factors associated with treatment failure in previous studies include age, performance status, comorbidities [4], and disease status at the time of transplant [5]. Because of increasing NRM with advanced age, conventional myeloablative HCT is usually restricted to patients under 55 to 60 years of age, with good performance status and preserved organ function. In older or more debilitated patients, the use of reduced-intensity conditioning (RIC) has been shown to be safer and thus has increased access to alloHCT for these patients [6-8].

Of all the potential sources of allografts, alloHCT from a HLA-matched sibling has generally produced the best overall outcomes. Unfortunately, only about a third of candidates for alloHCT have a matched related donor (MRD) [9]. For patients who lack an MRD, there are 3 alternative sources of stem cells for HCT: matched unrelated donor (MUD), umbilical cord blood and partially HLA-mismatched, or haploidentical, related donors (haplo). The probability of finding an 8/8 HLA identical MUD varies by racial/ethnic groups, ranging from 75% in white Europeans to 15% to 20% for African Americans and black Caribbeans [10]. In addition, MUD transplantation is also complicated by the amount of time it takes from search initiation to transplant, causing some patients to relapse or physically deteriorate while waiting for transplant. Because any patient shares exactly 1 HLA haplotype with each biologic parent or child and half of siblings, an eligible haplo donor can be identified rapidly in nearly all cases.

Financial disclosure: See Acknowledgments on page 1821.
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http://dx.doi.org/10.1016/j.bbmt.2016.07.010
1083-8791/

Although alloHCT is the most effective antileukemic therapy in patients with high-risk acute leukemia, the factors that are most important in transplant success are yet to be fully elucidated. This is particularly true in the modern era where alternative donors have become readily available and supportive care regimens have become more effective. Disease-related, host-related, and transplant-related factors may all be important in optimizing transplant outcomes. We analyzed 172 consecutively transplanted acute leukemia patients at our institution receiving a either a T cell–replete MRD, MUD, or haplo HCT to determine which risk factors most correlate with key transplant endpoints such as relapse, NRM, disease-free survival (DFS), and overall survival (OS). This analysis was restricted to a modern day cohort of patients, with a large proportion of alternative donor transplants, in the hopes of making the results most relevant to contemporary practice.

METHODS

Patients

One hundred seventy-two consecutive patients who underwent a T cell–replete alloHCT from a MRD, MUD, or haplo donor for acute leukemia (AML or ALL), transplanted in complete remission (CR) between March 2006 and December 2014, were included in this analysis. CR was defined as patients with less than 5% blasts in the marrow, adequate blood count recovery (absolute neutrophil count > 1000/μL and platelet count > 100,000/μL), and without any definitive evidence of residual disease by flow cytometry or cytogenetic/FISH testing. Recipients of transplants incorporating ex vivo or in vivo T cell depletion were excluded from the analysis. Median follow-up for surviving patients was 38 months (range, 6 to 112) at the time of analysis. Baseline characteristics were prospectively recorded in our institutional database, and events (relapse, death, cause of death, occurrence, and grading of acute and chronic GVHD) were entered into the database in real time. These data were retrospectively extracted from the database at the time of analysis.

Transplant

A patient underwent transplantation using a haplo donor at our center if there was no available MRD or 8/8 HLA-A, -B, -C, or -DR identical MUD or if a suitable MRD or MUD was unavailable within the timeframe appropriate for the patient's malignancy and clinical circumstances. All patients without an available MRD underwent a MUD search and were categorized as a high, intermediate, or low probability search depending on the number of potential HLA-matched donors (>5, 1 to 5, 0, respectively). Patients with a high and low probability donor search were preferentially offered a MUD and haplo transplant, respectively. Patients with an intermediate probability donor search were prioritized to either MUD or haplo transplant at the discretion of the treating physician based on the perceived urgency of transplant and estimated time for successful MUD search.

Regimens were classified as myeloablative versus RIC or nonmyeloablative conditioning based on previously defined guidelines [11,12]. For purposes of statistical analysis, RIC regimens were combined with nonmyeloablative regimens and compared with myeloablative conditioning. MRD and MUD transplantations were performed using a variety of preparative regimens. Haplo transplants were performed following nonmyeloablative [13] or myeloablative [14,15] conditioning with post-transplant cyclophosphamide as previously published. No graft was subjected to ex vivo T cell depletion, and no patients received serotherapy for in vivo T cell depletion as part of their preparative regimen. Supportive care algorithms were identical for patients in the 3 donor groups. All patients were similarly managed in the outpatient setting, with admission reserved for complications or symptoms that could not be adequately managed without inpatient admission.

Definitions and Study Endpoints

Primary outcomes analyzed were OS, DFS (survival without evidence of active malignancy after transplantation), relapse of malignancy, and NRM. Acute GVHD was classified as clinically significant (grades II to IV) or severe (grades III to IV) [16]. Chronic GVHD was classified as mild, moderate, or severe by National Institutes of Health consensus criteria [17]. Acute and chronic GVHD were evaluated and graded by a single practitioner within the program. NRM and relapse were treated as competing risks.

Statistical Methods

Comparisons of patient characteristics between transplant groups and leukemia subtypes were performed using the Kruskal-Wallis test for continuous variables and the Fisher's exact test for categorical data. Cumulative incidences of NRM, relapse, acute GVHD, and chronic GVHD were computed to account for presence of competing risks [18]. Probabilities of OS and DFS were estimated using the Kaplan-Meier method. Cox regression analysis was performed on OS, DFS, relapse, and NRM. Donor type (MRD, MUD, haplo) was always included in the Cox models because the primary goal of the study was to investigate the impact of donor type on survival outcomes.

Other variables considered in multivariate analyses included age (<50 versus ≥50 years), race/ethnicity, diagnosis, disease status (first CR [CR1] versus second/third CR [CR2/3]), regimen type, regimen intensity (myeloablative versus nonmyeloablative/RIC), graft source (peripheral blood stem cells versus marrow), Karnofsky performance score (KPS; ≥90% versus <90%), Center for International Blood and Marrow Transplant Research/Dana-Farber revised disease risk index (DRI) [5], HCT-specific comorbidity index score [4] (≥3 versus 0 to 2), year of transplant, donor and recipient sex match (female donor and male recipient versus other), and time from diagnosis to transplant (<4 months, 4 to 6 months and >6 months). For the model of each outcome (relapse, NRM, DFS, OS), the variables were first selected by a backward stepwise selection procedure using a significance level of .05. The final models were constructed by including all variables significant for at least 1 outcome. Statistical analysis was performed using the software SAS (version 9.3, the SAS Institute, Cary, NC).

RESULTS

Patient and Graft Characteristics

Patient, disease, and transplant characteristics are listed in Table 1. Leukemia type included AML in 123 patients (CR1, 94; CR2/3, 29) and ALL in 49 (CR1, 39; CR2/3, 10). Median age of transplant recipients was 50 years (range, 19 to 74). Donor type included MRD (n = 54, 31%), MUD (n = 67, 39%), and haplo (n = 51, n = 30%). MUD donors were 8/8 HLA-matched in 64 of 67 patients (96%), and the remaining 3 MUD donors were 1 antigen/allele mismatched. Haplo donor–recipient pairs were HLA matched at 5/10, 6/10, 7/10, and 8/10 loci in 75%, 15%, 8%, and 2%, respectively. The few significant differences in patient, disease, or transplant characteristics between donor type (MRD, MUD, haplo) included race/ethnicity, time from diagnosis to transplant, regimen type, and stem cell source (Table 1). African American recipients constituted 43% of the haplo group versus 13% and 2% of the MRD and MUD groups, respectively. Of the 30 African American transplant recipients in this study, 7 (24%) had an available MRD, whereas 1 (3%) and 22 (73%) used MUD and haplo donors, respectively. Compared with AML patients, ALL patients were more likely to be younger (median age, 46 versus 52; $P = .002$), and to use full-dose total body irradiation (12 Gy) in the conditioning regimen (80% versus 15%, $P < .001$).

Relapse, DFS, and OS

After a median follow-up for surviving patients of 38 months, the estimated rates of 3-year OS, DFS, and cumulative incidence of relapse were 59%, 50%, and 33%, respectively. DFS, relapse, and NRM were not significantly different in regards to donor type (MRD, MUD, haplo) (Figure 1). Disease risk as measured by the DRI had a major impact on survival, with rates of OS and DFS of 66% and 55%, respectively, for patients with low/intermediate risk disease versus 35% and 34%, respectively, for patients with high risk disease ($P < .001$ and $P = .004$ for OS and DFS, respectively). Although 3-year OS was higher in younger patients, this did not achieve statistical significance (66% versus 52%, $P = .117$ for patients <50 years versus ≥50 years, respectively). Point estimates for 1- and 3-year survival and cumulative incidence of relapse according to leukemia type, transplant type, and age are presented in Table 2.

GVHD and NRM

Grades II to IV and III to IV acute GVHD occurred in 36% and 13% of patients, respectively. Chronic GVHD of any grade was seen in 48% and was clinically significant (moderate-to-severe) or severe in 37% and 20% of patients, respectively.