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Unrelated Donor Allogeneic Transplantation after Failure of Autologous Transplantation for Acute Myelogenous Leukemia: A Study from the Center for International Blood and Marrow Transplantation Research

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A B S T R A C T

The survival of patients with relapsed acute myelogenous leukemia (AML) after autologous hematopoietic stem cell transplantation (auto-HCT) is very poor. We studied the outcomes of 302 patients who underwent secondary allogeneic hematopoietic cell transplantation (allo-HCT) from an unrelated donor (URD) using either myeloablative (n = 242) or reduced-intensity conditioning (RIC; n = 60) regimens reported to the Center for International Blood and Marrow Transplantation Research. After a median follow-up of 58 months (range, 2 to 160 months), the probability of treatment-related mortality was 44% (95% confidence interval [CI], 38%-50%) at 1-year. The 5-year incidence of relapse was 32% (95% CI, 27%-38%), and that of overall survival was 22% (95% CI, 18%-27%). Multivariate analysis revealed a significantly better overal survival with RIC regimens (hazard ratio [HR], 0.51; 95% CI, 0.35-0.75; $P < .001$), with Karnofsky Performance Status score ≥90% (HR, 0.62; 95% CI, 0.47-0.82: $P = .001$) and in cytomegalovirus-negative recipients (HR, 0.64; 95% CI, 0.44-0.94; $P = .022$). A longer interval (>18 months) from auto-HCT to URD allo-HCT was associated with

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significantly lower riak of relapse (HR, 0.19; 95% CI, 0.09-0.38; $P < .001$) and improved leukemia-free survival (HR, 0.53; 95% CI, 0.34-0.84; $P = .006$). URD allo-HCT after auto-HCT relapse resulted in 20% long-term leukemia-free survival, with the best results seen in patients with a longer interval to secondary URD transplantation, with a Karnofsky Performance Status score ≥90%, in complete remission, and using an RIC regimen. Further efforts to reduce treatment-related mortality and relapse are still needed.

INTRODUCTION

Autologous hematopoietic bone marrow (BM) or peripheral blood (PB) stem cell transplantation (auto-HCT) can be an effective consolidation treatment associated with improved leukemia-free survival (LFS) in adults with acute myelogenous leukemia (AML) in randomized trials versus intensive consolidation chemotherapy [1-3]. The benefit of auto-HCT appears to be especially apparent in patients with favorable- and intermediate-risk AML [4,5] and in adults [6]. Post–auto-HCT treatment failure is related primarily to relapse, particularly within the first 2 years [7]. Relapse is reportedly more likely in recipients of PB grafts [8] and in patients who do not receive pretransplantation consolidation chemotherapy [9]. Unfortunately, survival in patients who relapse after auto-HCT is very poor [1,10]. Previous auto-HCT is associated with both a lower likelihood of achieving subsequent complete remission (CR) [10,11] and higher mortality, and has been identified as an independent adverse risk feature for survival in first relapsed AML [10]. In view of the poor outcomes with available therapies, patients who relapse after auto-HCT are candidates for alternative strategies or investigational therapy.

Some patients with relapsed AML undergo a secondary allogeneic hematopoietic cell transplantation (allo-HCT) after failure of auto-HCT, and long-term survival has been noted, although often limited by high treatment-related mortality (TRM) [12-19]. More recent reports have described the use of RIC or nonmyeloablative conditioning regimens (RIC/NMA) in an attempt to reduce TRM [20-26]. Patients in CR at the time of RIC/NMA appear to have significantly lower TRM and risk of relapse, as well as superior overall survival (OS). In limited series, similar OS was reported with RIC or myeloablative (MA) conditioning in this clinical setting [20,24].

Using the large multicenter observational database from the Center for International Blood and Marrow Transplantation Research (CIBMTR), we examined the outcomes of secondary unrelated donor (URD) allo-HCT in patients with AML who underwent previous unsuccessful auto-HCT, with the aim of identifying patients and HCT techniques most likely to be successful.

PATIENTS AND METHODS

Data Sources

The CIBMTR is a research affiliation of the International Bone Marrow Transplantation Registry, Autologous Blood and Marrow Transplantation Registry, and the National Marrow Donor Program. Established in 2004, the registry receives data from more than 450 transplantation centers worldwide on consecutive allo-HCTs and auto-HCTs with computerized checks for discrepancies, physicians' review of submitted data, and onsite audits of participating centers ensure data quality. The CIBMTR collects detailed clinical data pre-HCT, at 100 days and 6 months post-HCT, and annually thereafter.

Observational studies conducted by the CIBMTR are performed with approval of the Institutional Review Boards of the National Marrow Donor Program and the Medical College of Wisconsin.

Patient Population

A total of 302 patients were reported to the CIBMTR who underwent secondary URD allo-HCT for either relapsed or persistent AML after previous auto-HCT between 1995 and 2005. Patients undergoing allo-HCT using cord blood or related donors were excluded. Information on the previous auto-HCT and lines of therapy after relapse for those achieving subsequent CR was unavailable for the majority of the patients, and thus is not included in this analysis.

Conditioning Regimens

Conditioning and graft-versus-host disease (GVHD) prophylaxis regimens are shown in Table 1. CIBMTR definitions of MA and RIC/NMA conditioning regimens (predominantly fludarabine-based; see Table 1) and HLA matching were applied [27,28]. For HLA matching, "well matched" was defined as no known disparity at HLA-A, -B, -C, or -DRB1; "partially matched," as a known or likely disparity at 1 locus; and "mismatched," as a disparity at 2 or more loci [29]. AML cytogenetics before auto-HCT were categorized as "good," "intermediate," or "poor" risk according to the UK Medical Research Council classification scheme [30]. Patients with t(7;12)(q36;p13), t(16;21)(q24;q22), or del(5q)/del(7q) were included in the poor-risk group, and those with t(9;11) were included in the intermediate-risk group [30-32].

Endpoints

The primary outcomes studied were TRM, relapse, LFS, and OS. Secondary outcomes were hematopoietic recovery (neutrophil and platelet engraftment) and the incidence of grade III/IV acute GVHD (aGVHD) and chronic GVHD (cGVHD).

An event for LFS was death or hematologic relapse after allo-HCT, and an event for OS was death from any cause. Surviving patients were censored at the date of last contact. TRM was defined as any death occurring before leukemia relapse. Persistence of AML after allo-HCT was considered relapse at day +1 after allo-HCT.

Statistical Analysis

The analysis of outcomes after secondary URD allo-HCT considered patient-related factors (age, sex, race, cytomegalovirus [CMV] serostatus, Karnofsky performance status [(KPS] score, and serum bilirubin and creatinine levels) and disease-related factors (CR and cytogenetics), as well as variables related to previous auto-HCT (time from auto-HCT to relapse and to the secondary URD allo-HCT). Allo-HCT–related variables considered included donor age, race, sex, parity, and CMV status; PB versus BM graft and cell dose (total nucleated cells for BM and total $CD34^+$ cells for PB, if available); HLA matching and ABO compatibility; MA versus RIC/NMA conditioning; GVHD prophylaxis (T cell depletion versus no T cell depletion); use of growth factor post-HCT; and the incidence of aGVHD grade III/IV or cGVHD of any severity as time-dependent variables.

Kaplan-Meier estimates were determined for OS and LFS, and the incidence of TRM, relapse, and aGVHD and cGVHD were calculated using the cumulative incidence function to accommodate competing risks. Analyses were performed at a 5-year time point.

Multivariate analysis was conducted using the proportional hazards model. All models were examined to confirm compliance with the proportional hazards assumption, and no violations of this assumption were detected. A stepwise approach was then used to develop Cox regression models for OS, LFS, and time to relapse and TRM for those in CR. Interactions between significant variables in the model were also considered for all models.

RESULTS

Patient and Clinical Characteristics

A total of 302 patients who underwent secondary URD allo-HCT between 1995 and 2005 for AML progression after a previous auto-HCT were reported to the CIBMTR from 99 transplantation centers. The median patient age was 38 years (range, 1 to 65 years), 47% were male, and 90% were Caucasian (Table 1). The median time from auto-HCT to URD allo-HCT was 14 months (range 1 to 98 months), and this interval was >6 months in 86% of the patients. The majority (72%) of