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Hematologic Recovery after Pretransplant Chemotherapy Does Not Influence Survival after Allogeneic Hematopoietic Cell Transplantation in Acute Myeloid Leukemia Patients

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Pretransplant remission status in patients with acute myeloid leukemia (AML) is 1 of the most important factors determining their outcomes after allogeneic hematopoietic cell transplantation (allo-HCT). Most patients are in complete remission with full hematologic recovery (CR) before undergoing allo-HCT. However, some patients achieve CR without recovery of platelet count (CRp) or a morphologic leukemia-free state (MLFS), defined as meeting all CR criteria without recovery of both neutrophil and platelet counts. Currently, there is a paucity of data regarding transplant outcomes in AML patients achieving MLFS after chemotherapy. To address this question, we evaluated transplant outcomes in 270 AML patients who received 6/6 HLA-matched sibling or 10/10 HLA-matched unrelated donor transplantation at a single institution between 2006 and 2013. Of our 270 patients, 206 were in CR, 45 were in CRp, and 19 were in MLFS before allo-HCT. Patients in CR, CRp, or MLFS had similar 3-year overall survival rates (49%, 46%, and 47%, respectively; $P = .88$) and 3-year event-free survival rates (45%, 36%, and 40%, respectively; $P = .53$). However, the cumulative incidence of nonrelapse mortality was significantly higher in patients in MLFS compared with those in CR (58% versus 22%, $P = .0004$), whereas the cumulative incidence of relapse in patients in MLFS was significantly lower compared with those in CR (11% versus 36%, $P = .03$). Our results suggest that survival outcomes in AML patients are not influenced by degree of hematologic recovery before allo-HCT.

INTRODUCTION

Despite the advancements of biomedical knowledge and treatment of acute myeloid leukemia (AML), patients with AML continue to have poor survival outcomes, with 5-year overall survival (OS) rates still close to only 25%. The prognosis is worse for patients older than 60 years, whose 5-year OS rates are only 5% to 10% [1]. With new knowledge on molecular and genomic abnormalities, such as mutations in the *FLT3*, *TP53*, *IDH1/2*, *TET2*, and *MLL* genes, we also know these AML-specific factors affect overall prognosis [2-12].

In addition to age and genetic mutations, remission status after chemotherapy is also important in determining prognosis. Achievement of complete remission (CR) after induction treatment has been shown to correlate with improved survival in AML patients [13]. Part of the definition of CR requires hematologic recovery that include a platelet count greater than 100,000/μL and an absolute neutrophil count (ANC) greater than 1000/μL [14]. In contrast, studies have shown that CR with incomplete hematologic recovery is associated with reduced OS and increased risk of relapse [13,15-19]. However, most of these studies focused predominantly on patients who did not receive allogeneic hematopoietic cell transplantation (allo-HCT). Furthermore, there is currently a paucity of data on outcomes in AML patients who achieve a morphologic leukemia-free state (MLFS), defined as meeting all CR criteria except for

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hematologic recovery (platelet count < 100,000/μL and ANC < 1000/μL) [14,20].

It is currently a common practice to wait for complete hematologic recovery before proceeding with allo-HCT in most AML patients. However, this approach potentially increases the risk of infectious and noninfectious (bleeding, transfusion-related adverse events, etc.) complications, which could potentially make these patients ineligible for transplant and consequently jeopardize their chances of long-term survival. To address the question of whether achieving MLFS adversely affects survival and relapse in AML patients who undergo allo-HCT, we retrospectively analyzed the post-transplant outcomes of AML patients based on the extent of hematologic recovery after pretransplant chemotherapy.

METHODS

Study Population

The study included 503 consecutive AML patients who underwent their first allo-HCT at Washington University Medical Center in St. Louis between 2006 and 2013. This study was approved by the Institutional Review Board of Washington University School of Medicine, St. Louis.

Patient, donor, and transplant characteristics were collected and retrospectively entered into the Washington University School of Medicine Blood and Marrow Transplant Database. Of the 503 patients, data from 270 patients were analyzed based on the following eligibility criteria: (1) 6/6 match at HLA loci A, B, and DRB1 by low-resolution genotyping [21] in related donor transplantation or 10/10 match at HLA loci A, B, C, DRB1, and DQB1 by high-resolution genotyping [22] in unrelated donor transplantation; (2) use of unmodified stem cells/nonmanipulated grafts; and (3) no evidence of active disease (bone marrow blasts < 5%) based on last bone marrow biopsy before transplant.

The type of conditioning regimen was classified based on consensus definition of conditioning regimen intensity [23]. Reduced-intensity and nonmyeloablative regimens were grouped together under the reduced-intensity conditioning (RIC) cohort. The HCT-specific comorbidity index (HCT-CI) score was calculated for all patients and categorized into 3 risk groups: low risk defined as score of 0, intermediate risk defined as score of 1 to 2, and high risk defined as score of 3 or greater [24].

Definitions

Based on hematologic recovery before initiating pretransplant conditioning, patients were classified into 3 cohorts: (1) CR, (2) CR with incomplete platelet count recovery (CRp), and (3) MLFS. CR was defined as follows: (1) bone marrow blasts less than 5%, (2) ANC greater than 1000/μL, (3) platelet count greater than 100,000/μL, (4) absence of blasts with Auer rods, (5) absence of extramedullary disease, and (6) independence of RBC transfusions, according to response criteria from the International Working Group [14]. CR was not further classified into cytogenetic CR or molecular CR. CRp was defined as meeting all CR criteria except for platelet count less than 100,000/μL. MLFS was defined as meeting all CR criteria except for a combination of ANC less than 1000/μL and platelet count less than 100,000/μL. Pretransplant bone marrow was also evaluated for the persistence of cytogenetic (ie, translocations, chromosomal deletions) and molecular (ie, *FLT3*, *NPM1*, *CEBPA* mutations) abnormalities present at the time of original diagnosis.

Acute graft-versus-host disease (aGVHD) was diagnosed based on signs and symptoms and graded according to accepted criteria [25]. Chronic GVHD (cGVHD) was graded using National Institutes of Health consensus criteria [26].

Etiology of AML was classified into (1) de novo AML or (2) secondary AML, defined as occurring from treatment (radiation, alkylating agents, topoisomerase inhibitors) and bone marrow disorders such as myeloproliferative neoplasm or myelodysplastic syndrome [14,27]. AML was classified into good, intermediate, and poor prognostic cohorts based on the European LeukemiaNet classification scheme for cytogenetic and molecular genetic data [20].

Post-Transplantation Disease Monitoring

Engraftment of the donor cells was determined by PCR assay for short tandem repeats or fluorescence in situ hybridization from bone marrow samples and/or peripheral blood mononuclear cells [28]. Complete donor engraftment was defined as the presence of less than 5% of recipient cells at 30 days after transplant. Mixed chimerism was defined as presence of greater than 5% but no more than 95% of recipient cells. Patients underwent bone marrow biopsies after allo-HCT at 30 days and 100 days and then every 6 months or earlier if peripheral blood counts showed abnormal findings of concern for relapse. Disease in remission after transplant was defined as absence of excess blasts on bone marrow biopsy 30 days after transplant. Extramedullary disease or relapse was defined by presence of blasts in tissue biopsy or cerebrospinal fluid.

Study Endpoints and Statistical Analysis

The study end points included 3-year OS, 3-year event-free survival (EFS), and cumulative incidences of relapse, nonrelapse mortality (NRM), aGVHD, and cGHVD. OS was defined as the time from transplant to death from any cause or last follow-up. Those patients alive were censored at the last follow-up. EFS was defined as the time from transplant to relapse or death without relapse, whichever occurred first, whereas those patients alive and free of disease were censored at the last follow-up [14].

The distributions of demographic and clinical characteristics across the 3 cohorts (CR, CRp, and MLFS) were compared using the chi-square test, Kruskall-Wallis rank-sum test, or 1-way analysis of variance as appropriate. Survival curves by remission status were estimated using the Kaplan-Meier product-limit method, and the differences in OS or EFS at 3 years were compared using Klein's pseudo-value approach [29]. To assess whether remission status was an independent predictor of OS and EFS, propensity-score matching was used to adjust for potential confounding effects of patient characteristics [30]. The propensity scores for achieving CR were estimated using multivariate logistic regression, including age, donor–patient sex mismatch, disease etiology, disease status at transplant, disease classification by cytogenetics, conditioning regimen, transplant type, and antithymocyte globulin regimen. A 3:1 matching (eg, identifying 3 matched patients from a CR cohort for every patients in MLFS cohort) was used for comparing CR versus MLFS cohorts, whereas a 1:1 matching was used for CR versus CRp cohorts. The cumulative incidences of NRM and relapse were calculated using Gray's subdistribution method to account for the presence of competing risks [31].

All analyses were 2-sided, and significance was set at $P = .05$. Statistical analyses were performed using statistical packages cmprsk (http://bio-www.dfci.harvard.edu/~gray) for competing risk analysis and SAS 9.3 (SAS Institutes, Cary, NC) for all other analyses.

RESULTS

Patient Characteristics

The distribution of patients among these cohorts was as follows: 206 in CR, 45 in CRp, and 19 in MLFS. Patient, disease, and transplant characteristics of these cohorts are summarized in Table 1. In our entire patient cohort, the median age was 54 years (range, 17 to 74). There was no significant difference in median age or time between last chemotherapy and transplant among the 3 individual cohorts. Likewise, there was no significant difference in distribution by gender, disease prognosis, disease etiology, and type of transplant. There were 5 significant differences between the cohorts. First, there were more female donor–male recipient transplants in the MLFS cohort than in the CR and CRp cohorts ($P = .007$). Second, a lower percentage of patients in the CRp cohort underwent a myeloablative conditioning regimen than in the CR and MLFS cohorts ($P = .024$). Third, a higher percentage of patients in the CRp cohort had a high HCT-CI score (3 or greater) than in the CR and MLFS cohorts ($P = .024$). Fourth, a higher percentage of patients in the MLFS cohort had pretransplant bone marrow cellularity of 10% or less than in the CR or CRp cohorts ($P < .001$). However, the range of bone marrow cellularity was wide in all cohorts, with a maximum cellularity of 80% in the MLFS cohort, 90% in the CR cohort, and 70% in the CRp cohort (data not shown). Fifth, there was a higher percentage of patients in the MLFS cohort who had persistent cytogenetic and/or molecular abnormalities in pretransplant bone marrow ($P < .001$).

The types of chemotherapy regimens immediately before transplant were relatively similar in distribution for the 3 cohorts, except that high-dose cytarabine was less commonly used in the MLFS cohort than in the CR and CRp