Clinical Research

Benefit of Allogeneic Transplantation in Patients Age ≥ 60 Years with Acute Myeloid Leukemia Is Limited to Those in First Complete Remission at Time of Transplant

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A B S T R A C T

We evaluated the impact of age and remission status on 242 consecutive patients who underwent allogeneic hematopoietic cell transplantation for acute myeloid leukemia (AML) in our program between 1999 and 2011. Median age of all patients was 48 years (range, 18 to 71). Based on age and remission status, patients were divided into 4 groups: first complete remission (CR1) age <60 years (n = 116), second complete remission (CR2) age <60 years (n = 78), CR1 age ≥60 years (n = 32), and CR2 age ≥60 years (n = 16). Donors were matched related (n = 155, 64%) or matched unrelated (n = 87, 36%). Median follow-up of survivors was 65 months (range, 12 to 145). In a univariate analysis, 3-year overall survival rates of the 4 groups were 57%, 43%, 39%, and 16% (P = .003), respectively. In a multivariable analysis, hazard ratios of nonrelapse mortality and survival were 2.08 (P = .06) and 1.52 (P = .23), respectively, in patients ≥60 years in CR2 compared with ≥ 60 years in CR1. Although a plateau in survival was observed for patients ≥60 years in CR1 similar to those <60 years in CR1 and CR2, no long-term survivors were seen in patients ≥60 years in CR2. Our data suggest disappointing outcomes in AML patients ≥60 years of age transplanted in CR2. Therefore, if a transplant is indicated, early referral is recommended in patients ≥60 years with AML.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) offers curative potential in the treatment of patients with acute myeloid leukemia (AML). The advantage of HCT compared with conventional chemotherapy for subgroups of AML patients was previously reviewed [1]. A meta-analysis demonstrated improved survival in patients aged ≤ 60 years with AML in first complete remission (CR1) with intermediate or adverse cytogenetics at diagnosis who underwent HCT compared with those who received conventional chemotherapy [2]. The benefit of HCT for younger patients was recently demonstrated in patients with AML in second complete remission (CR2), who had intermediate- or adverse-risk cytogenetics [3].

The outcomes of younger patients with AML have improved in the last 2 decades. Factors contributing to improved outcomes in younger patients with AML include improvements in supportive care and increased utilization as well as optimization of HCT [4]. Although outcomes of younger patients with AML have improved, no significant improvement has been observed in older patients [5]. A case-

controlled study showed improved outcome of patients ages 60 to 70 years treated with HCT compared with chemotherapy alone [6].

In transplant recipients, some studies demonstrated that older age alone did not significantly affect survival post-transplant but remission status did, with a significant advantage for patients transplanted in CR1 [7]. On the contrary, another study showed that remission status did not affect survival of patients with AML post-HCT using reduced-intensity conditioning (RIC); however, this study included patients with a wide range of ages, including younger patients [8]. A Center for International Blood and Marrow Transplant Research study showed that older patients undergoing RIC HCT for AML in CR1 benefit as equally as younger patients [9]. Reports in the literature concerning the benefit of older patients (≥60 years) in CR2 are conflicting. Some studies demonstrated a lack of significant effect of patient age on outcome [10,11], whereas others found that patient age ≥55 years is a predictor of poor survival after HCT for AML in CR2 [12].

We evaluated the impact of age in association with remission status on the outcomes of 242 consecutive patients who underwent HCT for AML in our program from 1999 to 2011. We report that HCT offers a curative potential to AML patients ≥60 years in CR1 similar to younger patients; however, the outcomes in patients ≥60 years in CR2 are disappointing. We also explore the causes for poor outcomes

in these patients to guide practice improvements for the future.

METHODS
Patients

The study population consisted of 242 consecutive patients aged 18 to 71 years undergoing first allogeneic transplant for AML in CR1 and CR2 from matched related (n = 155) or matched unrelated donors (n = 87) between January 1999 and June 2011 at Princess Margaret Cancer Centre, Toronto, Ontario, Canada. Among these patients, 194 (80%) were age <60 at transplant, and 48 (20%) were age ≥60 years. Data were collected from the Electronic Patient Records of the hospital as well as the Bone Marrow Transplant Program database. The study was approved by the Cancer Registry Data Access Committee and the Research Ethics Board of the University Health Network/Princess Margaret Cancer Centre (REB no. 12-0048-CE).

Data

Data collected and subsequently analyzed involved a number of pre-transplant variables, including age, gender, cytogenetic risk at diagnosis, conditioning regimen, hematopoietic progenitor cell source, related or un-related donor status, and cytomegalovirus serostatus of donor and recipient. Based on age and remission status, patients were divided into 4 groups: CR1 age <60 years, CR2 age <60 years, CR1 age ≥60 years, and CR2 age ≥60 years. Cytogenetics at diagnosis was characterized as favorable, inter-mediate, unfavorable, and unknown risk as previously described [13].

The HCT-comorbidity index was calculated for all transplanted patients retrospectively from the pretransplant investigations and chart review. Comorbidities were analyzed as presenting with either a low-risk (0 to 2) or high-risk score (≥3) [14].

Conditioning Regimens and Graft-versus-Host Disease Prophylaxis

Patients were conditioned either with myeloablative conditioning or RIC regimens. The decision to offer RIC was primarily based on patient age and the presence of significant comorbidities, as previously described [15]. Classification of the intensity of conditioning regimen was based on the Center for International Blood and Marrow Transplant Research suggested criteria [16]. The myeloablative conditioning regimens were subdivided into 2 groups. First, those used from 1999 to 2006 included busulfan 3.2 mg/kg for 4 days and cyclophosphamide 60 mg/kg for 2 days cyclophosphamide 60 mg/kg for 2 days and total body irradiation 12 Gy. Second, since 2006 patients received conditioning with fludarabine 50 mg/m^2 for 4 days, busulfan 3.2 mg/kg for 4 days, and total body irradiation 400 cGy in 2 fractions.

RIC regimens used between 1999 and 2006 included combinations of fludarabine 30 mg/m^2 for 4 to 5 days with busulfan 3.2 mg/kg for 2 days or with total body irradiation 200 cGy [17]. Since 2006 patients were condi-tioned with fludarabine 30 mg/m^2 for 4 days, busulfan 3.2 mg/kg for 2 days, and total body irradiation 200 cGy.

Graft-versus-host disease prophylaxis consisted of cyclosporine A, combined with either methotrexate (15 mg/m^2 on HCT day +1 and 10 mg/m^2 on HCT days +3, +6, and +11; n = 124) or mycophenolate mofetil (given for 28 days post-transplant; n = 60). Serotherapy using low-dose alemtu-zumab or antithymocyte globulin was used in combination with cyclo-sporine A in 58 patients undergoing unrelated donor transplantation.

Definitions of Clinical Endpoints

For the purpose of this study, complete remission (CR) was defined as achievement of a bone marrow with <5% blasts and count recovery. Relapse was defined as ≥5% blasts in a bone marrow aspirate or peripheral blood or the development of extramedullary leukemia after transplant. Overall sur-vival (OS) times were measured from the date of HCT until death from any cause. Alive patients were censored on the date of their last follow-up. Leukemia-free survival (LFS) was defined as the time from transplantation to relapse or death from any cause. Nonrelapse mortality (NRM) was calculated as death without evidence of disease relapse.

Statistical Analysis

Patient demographics and treatment-related outcomes were reported using descriptive statistics. Categorical variables were summarized with counts and percentages. Continuous variables were summarized with means and/or medians with ranges. Data were updated as of June 2012.

Contingency statistics using the chi-square test or Fisher's exact test (as appropriate) were performed for the comparison of distribution of the variables between the four groups defined by CR status/age combination. Analysis of variance was used to compare the continuous outcome age at transplant among the 4 groups.

The main outcome variables of interest were death due to any cause OS, LFS, cumulative incidence of relapse CIR, and cumulative incidence of NRM. OS and LFS were calculated using the Kaplan-Meier product-limit method. The log-rank test was used as a univariate analysis to compare the levels of the 4 groups consisting of age/CR status combination as well as baseline patient characteristics. CIR and NRM were calculated using the competing risk method based on Pepe and Mori's method [18]. The Fine and Gry method for competing risks was used for univariate and multivariable an-alyses in comparing CIR and NRM.

Because of the small sample size, we performed a limited multivariable analysis using clinically relevant factors. The following factors were analyzed: age/remission status (<60 in CR1, <60 in CR2, ≥60 in CR1, and ≥60 in CR2), donor type (related versus unrelated), conditioning regimen (myeloablative conditioning versus RIC), HCT-comorbidity index score (0 to 2 versus ≥3), and time period of HCT (before or after 2006, which was when different conditioning regimens were used as described previously). Results were considered significant if $P < .05$. Statistical analyses were performed using version 9.2 of the SAS system and user's guide (SAS Institute, Inc., Cary, NC) and R version 2.14.0, the R foundation for statistical computing.

RESULTS
Patient and Transplant Characteristics

Baseline patient, disease, and transplant-related charac-teristics are summarized in Table 1. Two hundred forty-two patients with a median age of 48 years (range, 18 to 71) underwent transplantation. One hundred twenty-three pa-tients were male (51%), and peripheral blood stem cells were used in 178 patients (74%). Donors were matched related (n = 155, 64%) or matched unrelated (n = 87, 36%). Median follow-up of survivors was 65 months (range, 12 to 145).

The number of patients in each of the 4 groups based on age and remission status as previously defined was as fol-lows: 116 patients (48%) transplanted in CR1 age <60, 78 patients (32%) in CR2 age <60, 32 patients (13%) in CR1 age ≥60, and 16 patients (7%) in CR2 age ≥60. Among the study patients, 170 (70%) received myeloablative condition-ing regimens and 72 patients (30%) RIC regimens. Of the 48 patients ≥60 years of age, 46 (96%) received RIC regimens. Of the 194 patients <60 years of age, 26 (13%) received RIC regimens.

Primary Endpoints
Overall survival

Univariate comparison between the 4 groups divided by age/remission status (<60 in CR1, <60 in CR2, ≥60 in CR1, and ≥60 in CR2) demonstrated a significant difference in survival ($P = .003$) (Figure 1a). OS at 3 years for the 4 groups was 57% (95% confidence interval [CI], 48% to 66%), 43% (95% CI, 32% to 54%), 39% (95% CI, 22% to 56%), and 16% (95% CI, 3% to 38%), respectively. The hazard ratios (HRs) for survival for the groups <60 CR1, <60 CR2, and ≥60 CR2 compared with group ≥60 CR1 were .67 ($P = .13$), 1.03 ($P = .91$), and 1.83 ($P = .08$), respectively. Of the other variables studied, unre-lated donor status carried an increased risk ($P = .04$; HR, 1.44) and an HCT-comorbidity index score ≥3 ($P = .02$; HR, 1.55). In the univariate analysis, cytogenetic risk at diagnosis, gender, cytomegalovirus serostatus, graft source, conditioning in-tensity, and year of transplant during/after 2006 were not statistically significant for OS.

A limited multivariable analysis was performed for OS using the parameters age/remission status, donor type, conditioning regimen, HCT-comorbidity index score, and year of transplant during/after 2006. Age/remission status group had a significant effect on OS (overall $P = .02$). HRs for the groups <60 CR1, <60 CR2, and ≥60 CR2 in reference to group ≥60 CR1 were .47, .61, and 1.52, respectively. Trans-plant performed during/after 2006 influenced OS favorably ($P = .04$; HR, .67). Donor status, conditioning regimen, and