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Outcomes of Human Leukocyte Antigen–Matched Sibling Donor Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia: Myeloablative Versus Reduced-Intensity Conditioning Regimens

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A B S T R A C T

Allogeneic hematopoietic cell transplantation (HCT) can cure some chronic lymphocytic leukemia (CLL) subjects. This study compared outcomes of myeloablative (MA) and reduced-intensity conditioning (RIC) transplants from HLA-matched sibling donors (MSD) for CLL. From 1995 to 2007, information regarding 297 CLL subjects was reported to the Center of International Blood and Marrow Transplant Research; of these, 163 underwent MA and 134 underwent RIC MSD HCT. The MA subjects underwent transplantation less often after 2000 and less commonly received antithymocyte globulin (4% versus 13%, $P = .004$) or prior antibody therapy (14% versus 53%; $P < .001$). RIC was associated with a greater likelihood of platelet recovery and less grade 2 to 4 acute graft-versus-host disease compared with MA conditioning. One- and 5-year treatment-related mortality (TRM) were 24% (95% confidence intervals [CI], 16% to 33%) versus 37% (95% CI, 30% to 45%; $P = .023$), and 40% (95% CI, 29% to 51%) versus 54% (95% CI, 46% to 62%; $P = .036$), respectively, and the relapse/progression rates at 1 and 5 years were 21% (95% CI, 14% to 29%) versus 10% (95% CI, 6% to 15%; $P = .020$), and 35% (95% CI, 26% to 46%) versus 17% (95% CI, 12% to 24%; $P = .003$), respectively. MA conditioning was associated with better progression-free (PFS) (relative risk, .60; 95% CI, .37 to .97; $P = .038$) and 3-year survival in transplantations before 2001, but for subsequent years, RIC was associated with better PFS and survival (relative risk, 1.49 [95% CI, .92 to 2.42]; $P = .10$; and relative risk, 1.86 [95% CI, 1.11 to 3.13]; $P = .019$).

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Pretransplantation disease status was the most important predictor of relapse ($P = .003$) and PFS ($P = .0007$) for both forms of transplantation conditioning. MA and RIC MSD transplantations are effective for CLL. Future strategies to decrease TRM and reduce relapses are warranted.

INTRODUCTION

Myeloablative (MA) allogeneic hematopoietic cell transplantations (HCT) in persons with advanced chronic lymphocytic leukemia (CLL) have relapse rates of 10% to 20% [1-6]. However, treatment-related mortality (TRM) is 30% to 40% [1,3,6,7]. Because the majority of patients with CLL are older and have comorbidities, reduced-intensity conditioning (RIC) transplantations are an attractive option.

RIC allogeneic transplantations have successfully been performed for CLL with durable long-term survival [8-14]. They are associated with less toxicity and less early TRM compared with MA conditioning. RIC also can prevent relapse in subjects with advanced CLL, with complete response rates of 40% to 55% and progression-free survival (PFS) of 40% [8,13-15].

RIC transplantations are increasingly used, but no large series has compared outcomes with transplantations with MA conditioning. We analyzed the outcomes of HLA-matched sibling donor (MSD) RIC and MA conditioning approaches for persons with advanced CLL reported to the Center of International Blood and Marrow Transplant Research (CIBMTR).

PATIENTS AND METHODS

Data Sources

The CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. CIBMTR comprises a voluntary network of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous HCT to a centralized Statistical Center. Observational studies conducted by CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule. Additional details regarding the data source are described elsewhere [16].

Subject Eligibility

Subjects 40 to 59 years old with advanced CLL receiving a first HLA-MSD transplantation between 1995 and 2007 were eligible for the study. This age range was selected to make a more balanced comparison between the RIC and MA cohorts. Of 1260 CLL subjects reported to the CIBMTR during this time, 163 MA and 134 RIC HLA-MSD transplantations were reported. Data on disease-specific variables were not collected on unrelated donor HCT during study years; therefore, unrelated donor HCT recipients were excluded. Other exclusions include twin transplantations, HLA-haploidentical and umbilical cord blood transplantations, and those using ex vivo T cell–depleted grafts. No subjects received a prior autologous or allogeneic transplantation. The respective 3- and 5-year follow-up completeness index for data reported to the CIBMTR on study subjects were 86% and 76% [17].

Study Endpoints

Coprimary endpoints were PFS and survival. Secondary endpoints included hematopoietic recovery, TRM, acute and chronic graft-versus-host disease (GVHD), and relapse/progression. *Survival* was defined as time to death from any cause. Subjects were censored at time of last follow-up. *Relapse/progression* was defined as reported by the transplantation centers and TRM was considered a competing event. *TRM* was defined as death within the first 28 days of transplantation from any cause or death without evidence of recurrence; relapse was considered a competing event. *PFS* was defined as time to treatment failure (death or relapse). For relapse, TRM, and PFS, subjects alive in continuous complete remission were censored at last follow-up. *Hematopoietic recovery* was defined as time to absolute neutrophil count $>.5 \times 10^9$/L for ≥ 3 consecutive days and time to platelets $> 20 \times 10^9$/L without transfusions for 7 days, using the first of 3 consecutive results obtained on different days. Acute and chronic GVHD were diagnosed and graded using consensus criteria [18,19]. For hematopoietic recovery and GVHD, death without the event was considered a competing event.

Rai stage was determined as previously described [20]. *Fludarabine failure* was defined as not meeting criteria for partial or complete response after such therapy. The transplantation conditioning regimen intensity was determined according to the CIBMTR RIC Regimen Workshop [21].

Statistical Analysis

PFS and survival curves were estimated by the Kaplan-Meier method [22]. Patient-, disease-, and transplantation-related factors were compared between groups using the Chi-square test for categorical variables and the Wilcoxon 2-sample test for continuous variables. Cumulative incidence estimates to account for competing risks were calculated for hematopoietic recovery, TRM, acute and chronic GVHD, and disease relapse/progression. Cox proportional hazards regression was used to compare MA and RIC regimens. The assumption of proportional hazards for each factor in the Cox model was tested using time-dependent covariates. The multivariate model was built using a stepwise model selection approach. The main effect variable was MA versus RIC. The following variables were analyzed for their prognostic value on each of the outcomes: patient characteristics (age, sex, and Karnofsky performance status [KPS]), disease characteristics (Rai stage at diagnosis and at transplantation, constitutional symptoms, lactate dehydrogenase at transplantation, spleen status, and disease status at transplantation), and transplantation-related factors (time from diagnosis to HCT, donor age, donor-recipient gender and cytomegalovirus serology, GVHD prophylaxis regimen, and year of HCT). First order interactions between main effect and significant covariates were tested. In particular, because the year of transplantation was confounded with the main effect, the interaction between them was checked for all endpoints. For survival and PFS, an interaction between the main effect and year of HCT was found. The cut-off for year of HCT was determined using the maximum partial likelihood method. Factors significantly associated with the outcome variable at a 5% level were kept in the final model. All P values were 2-sided.

RESULTS

Transplantation Subjects

Subject- and disease-related characteristics are shown in Table 1. Subjects who received RIC transplantations were older, but with comparable baseline KPS compared with those who received MA regimens. The MA group less commonly received prior antibody therapy (19 [14%] versus 40 [53%], $P < .001$). No differences were found between the groups regarding disease that was refractory to fludarabine or antibody therapy before transplantation.

From the maximum partial likelihood method, a 2000 cut-off for year of HCT was chosen for subsequent analyses. When considering patient- and disease-related characteristics for those who underwent transplantation in 2000 or earlier, the only differences between the MA and RIC subjects were median age (49 years [range, 40 to 59 years] versus 53 years [40 to 59 years], $P < .001$), prior antibody therapy (2% versus 25%, $P < .001$), graft source (blood: 47% versus 89%, $P < .001$), and median donor age (47 years [27 to 65 years] versus 52 years [37 to 65 years], $P = .006$). Compared with the MA subjects, the RIC group more commonly received antithymocyte globulin (ATG) for conditioning or GVHD prophylaxis (15% versus 2%, $P = .005$) and less commonly received methotrexate for GVHD prophylaxis (26% versus 79%, $P < .001$).

For subjects who underwent transplantation after 2000, the patient- and disease-related characteristics were comparable between the MA and RIC subjects, except for the following respective differences: median age (51 years [range, 40 to 59 years] versus 54 years [42 to 59 years], $P = .005$) and graft source (blood: 92% versus 99%, $P = .024$).