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Allogeneic Hematopoietic Cell Transplantation for Adult T Cell Acute Lymphoblastic Leukemia

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A B S T R A C T

Allogeneic hematopoietic cell transplantation (HCT) is recommended for patients with T cell acute lymphoblastic leukemia (T-ALL) in second or later complete remission (CR) and high-risk patients in first CR. Given its relative rarity, data on outcomes of HCT for T-ALL are limited. We conducted a multicenter retrospective cohort study using data from 208 adult patients who underwent HCT between 2000 and 2014 to describe outcomes of allogeneic HCT for T-ALL in the contemporary era. The median age at HCT was 37 years, and the majority of patients underwent HCT in CR, using total body irradiation (TBI)-based myeloablative conditioning regimens. One-quarter of the patients underwent alternative donor HCT using a mismatched, umbilical cord blood, or haploidentical donor. With a median follow up of 38 months, overall survival at 5 years was 34%. The corresponding cumulative incidence of non-relapse mortality and relapse was 26% and 41%, respectively. In multivariable analysis, factors significantly associated with overall survival were the use of TBI (HR, 0.57; $P = .021$), age >35 years (HR, 1.55; $P = .025$), and disease status at HCT (HR, 1.98; $P = .005$ for relapsed/refractory disease compared with CR). Relapse was the most common cause of death (58% of patients). Allogeneic HCT remains a potentially curative option in selected patients with adult T-ALL, although relapse is a major cause of treatment failure.

INTRODUCTION

T cell acute lymphoblastic leukemia (T-ALL) is an aggressive precursor lymphoid neoplasm that accounts for only ~20% to 25% of all cases of adult ALL [1,2]. Although T-ALL is often

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studied in conjunction with and treated similarly as B cell acute lymphoblastic leukemia (B-ALL), T-ALL has distinct clinical, immunologic, cytogenetic, and molecular characteristics [1,3]. Data on this relatively rare disease remain limited, including the optimal therapeutic strategies. Allogeneic hematopoietic cell transplantation (HCT) is typically recommended for adults with T-ALL in second or later complete remission (CR2+), but also may be offered to patients in first CR (CR1) with high-risk features. There have been few reports on allogeneic HCT for the treatment of T-ALL [4-6]. In a prospective cohort of 356 adults with T-ALL treated uniformly between 1993 and 2006 on the Medical Research Council UKALL XII/Eastern Cooperative Oncology Group 2993, a donor/no-donor comparison demonstrated superior 5-year survival in patients with matched sibling donors compared with those without donors (61% versus 46%; $P = .02$), as a result of less relapse (25% versus 51% at 5 years; $P < .001$) [1]. Among the 107 patients undergoing allogeneic HCT in that study, the majority (82%) had an HLA-identical sibling donor, and all patients received a myeloablative conditioning (MAC) regimen. We conducted a multiinstitutional retrospective cohort study to evaluate outcomes of adults with T-ALL undergoing allogeneic HCT in the contemporary era of transplantation in older adults, reduced-intensity conditioning (RIC) regimens, and increasing use of matched unrelated and alternative donors.

PATIENTS AND METHODS

Data on patient characteristics and post-transplantation outcomes for consecutive adult patients with T-ALL undergoing allogeneic HCT were obtained from 13 transplantation centers in the United States and Canada. Patients were eligible if they had T-ALL confirmed by immunophenotyping, were age ≥17 years at the time of transplantation, and had undergone transplantation between 2000 and 2014. Patients undergoing HCT with any donor/graft source with either an MAC or an RIC regimen were eligible for enrollment. HCT was performed for high-risk T-ALL, generally defined as CR2+ or relapse, or CR1 with high-risk features (age ≥35 years, white blood cell [WBC] count at presentation of ≥100,000/mm^3, residual disease in bone marrow at day 15 postinduction, central nervous system [CNS] involvement, high-risk cytogenetic features, and/or need for >1 induction regimen to achieve CR1). CR was generally defined by morphologic criteria. The participating centers contributed deidentified data to the Cleveland Clinic, which served as the coordinating site. The study was conducted under guidance of the Cleveland Clinic's Institutional Review Board.

Outcomes were estimated from the date of transplantation and included overall survival (OS), relapse, relapse mortality, nonrelapse mortality (NRM), acute graft-versus-host disease (GVHD), and chronic GVHD. OS was estimated using the Kaplan-Meier method and compared using the log-rank test; all other outcomes were estimated using the cumulative incidence method. Risk factors were identified with Fine-Gray regression (relapse mortality and NRM) or Cox proportional hazards analysis (OS). Stepwise selection was used to identify multivariable risk factors. Variables included age at transplantation, sex, race, year of diagnosis, WBC count at diagnosis, marrow blast count at diagnosis, cytogenetic risk, CNS involvement, presence of extramedullary disease, time from diagnosis to HCT, performance status, HCT comorbidity index (HCT-CI) risk, recipient cytomegalovirus (CMV) status, disease status at HCT, conditioning intensity, use of TBI, hematopoietic cell source, and donor type. Age was analyzed as both a continuous variable and a categorical variable using ≥35 years as a cutoff. There was a strong association between number of previous chemotherapy regimens and disease status at transplantation, and the multivariate models included only the latter. To assess for center effect, we performed recursive partitioning analysis for the 13 sites relative to OS and identified 2 groups (best survival and worst survival); these were then adjusted for in the multivariable analysis for all outcomes. The final multivariable models included 5 variables that were significant for at least 1 mortality outcome: site, age >35 years, disease status, donor source, and TBI-based conditioning.

The results of multivariable analyses are presented as hazard ratio (HR) with 95% confidence interval (CI). The proportional hazards assumption was tested and found to be valid for all variables and outcomes except previous chemotherapy and relapse mortality. As noted earlier, disease status was used instead of previous chemotherapy in the analysis. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). All reported P values are 2-sided, and a P value of <.05 was considered to indicate significance.

RESULTS

A total of 208 patients from 13 transplantation centers were included in this study (Table 1). The median age at HCT was 37 years (range, 17 to 72 years). Most patients presented with a WBC count $<100 \times 10^9$/L at diagnosis (80%; 146 of 183). More than one-half (55%) had an abnormal karyotype at diagnosis, and 59% had extramedullary disease (including 12% with CNS involvement). Patients received HCT primarily while in CR (43% in CR1 and 39% in CR2+). Most patients received a MAC regimen (84%), and 86% of the regimens incorporated total body irradiation (TBI). Alternative donor transplants included HLA-mismatched unrelated donor (9%), umbilical cord blood (12%), and haploidentical donor with post-transplantation cyclophosphamide (5%). Seven percent of patients underwent HCT under an ex vivo T cell depletion protocol at one center. The median follow-up among surviving patients was 38.2 months (range, 0.4 to 186.5 months).

Table 2 summarizes outcomes, including those of selected clinically relevant subgroups by age, disease status, conditioning regimen, use of TBI, and donor source. Among all patients, 1-year survival was 58% (95% CI, 51% to 65%), and 5-year OS was 34% (95%, CI 27% to 41%). Relapse mortality was 24% (95% CI, 18% to 30%) at 1 year and 39% (95% CI, 32% to 47%) at 5 years, and NRM was 18% at 1 year (95% CI, 13% to 24%) and 27% at 5 years (95% CI, 21% to 34%) (Figure 1). The subset of patients age >35 years (5-year OS, 22%; 95% CI, 14% to 32%), patients with relapsed/refractory disease (5-year OS, 14%; 95% CI, 5% to 29%), and those who did not receive TBI (5-year OS, 12%; 95% CI, 2% to 29%) had the poorest survival. Recipients of grafts from alternative donor sources, including mismatched unrelated donors, haploidentical donors, and umbilical cord blood, had similar survival (34% OS at 5 years) compared with recipients of grafts from matched sibling and unrelated donors, but a higher NRMnon-relapse mortality (38% at 5 years). Of 125 patients who died, the most common cause of death was relapse (N = 72, 58%). Other causes of death included GVHD (N = 17, 14%), infection (n = 15, 12%), and organ toxicity/failure (n = 15; 12%).

Univariable risk factor analysis identified associations between TBI and better NRM (HR, 0.50; $P = .035$) and overall mortality (HR, 0.48; $P = .0001$), between relapsed/refractory disease and poorer relapse mortality (HR, 2.01; $P = .045$) and overall mortality (HR 2.33; $P < .001$), between age >35 years and poorer relapse mortality (HR, 1.82; $P = .019$) and overall mortality (HR, 1.63; $P = .009$), and between an alternative donor source and higher NRM (HR, 2.10; $P = .035$). In multivariable analysis, relapsed/refractory disease at transplantation remained significantly associated with worse overall mortality (HR, 1.98; 95% CI, 1.23 to 3.18; $P = .005$), as did age >35 years (HR, 1.55; 95% CI, 1.06 to 2.27; $P = .025$). The use of TBI (HR, 0.57; 95% CI, 0.36 to 0.92; $P = .021$) remained associated with better survival. Disease status (HR, 2.35; 95% CI, 1.25 to 4.44; $P = .008$ for relapsed/refractory disease) and age >35 years (HR, 1.81; 95% CI, 1.08 to 3.03; $P = .023$) also were significantly associated with higher relapse mortality, whereas having a matched unrelated donor (HR, 0.55; 95% CI, 0.31 to 0.99; $P = .045$) was associated with lower relapse mortality compared with having an HLA-identical sibling donor. The use of an alternative donor (HR, 2.17; 95% CI, 1.05 to 4.48; $P = .036$) was associated with increased NRM, however, whereas the use of TBI (HR, 0.51; 95% CI, 0.25 to 1.03; $P = .06$) trended toward decreased NRM.

The prognostic impact of TBI was further analyzed by disease status and intensity of conditioning. The majority of