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SUPPLEMENTARY DATA

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Abstract

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.

Keywords

Acute lymphoblastic leukemia; T cell; Hematopoietic cell; transplantation; Allogeneic; Survival; Relapse-free survival

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 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 patients underwent HCT with a TBI-based conditioning regimen (n = 176). Although only 30 patients received a non-TBI-based conditioning regimen, there was no difference in disease status between the 2 groups ($P = .25$). In the TBI group, 45% of the patients were in CR1, 38% were in CR2+, and 17% had relapsed/refractory disease. In the non-TBI group, 30% were in CR1, 43% were in CR2+, and 27% had relapsed/refractory disease. Within disease status subgroups, the prognostic impact of TBI was only statistically significant in the CR2+ group (n = 80) for NRM (HR, 0.25; $P = .001$) and overall mortality (HR, 0.47; $P = .030$). There was no statistically significant impact of TBI on the CR1 group (n = 88) or the relapsed/refractory group (n = 38). We also further evaluated the prognostic impact of TBI by intensity regimen. The majority of the cohort underwent MAC transplantation, and accordingly, similar to the entire cohort, TBI remained prognostically significant for better NRM (HR, 0.42; $P = .047$) and overall mortality (HR, 0.42; $P = .004$) in the MAC group, but not for the RIC group.

DISCUSSION

Treatment of T-ALL remains a challenge, and long-term outcomes in adult patients remain unsatisfactory. Studies focusing specifically on T-ALL are lacking owing to the disease's relative rarity, and thus prognostic factors for patients with T-ALL are much less well defined than those for patients with B-ALL. In our large contemporary cohort of T-ALL patients undergoing allogeneic HCT, including recipients of an RIC regimen and alternative donor HCT, one-third of the patients with high-risk disease survived for more than 5 years; however, relapse was the major cause of treatment failure. These data also identify disease status at transplantation as the most important risk factor for survival, confirming previous studies demonstrating the prognostic significance of achieving CR at the time of transplantation [4–6]. A single-institution study evaluated 53 patients with high risk T-ALL who underwent allogeneic HCT [4]. High risk was defined as patients in CR2+ or relapse or those in CR1 who were age ≥35 years, had a WBC count at presentation of ≥100,000/mm^3, had residual disease in the bone marrow at day 15 postinduction, had CNS involvement at diagnosis, had high-risk cytogenetic features, and/or required more than 1 induction regimen to achieve CR1. The median age was 18 years (range, 14 to 51 years), and all patients underwent MAC HCT. OS and disease-free survival (DFS) at 5 years were 43.5% and 41.8%, respectively, and were better for patients undergoing HCT in CR1 compared with those doing so in CR2+.

A recent study from the European Group for Blood and Marrow Transplantation of 601 patients with T-ALL found 5-year OS and leukemia-free survival of 45% and 41%, respectively. Survival also was better in patients undergoing HCT in CR1 compared to

≥CR2, with better survival in patients age <35 years receiving a TBI-based MAC regimen compared with those receiving a busulfan- or cyclophosphamide-based MAC regimen [5]. Although we observed no impact of specific conditioning regimen on survival, we also verified that the use of TBI in this disease was associated with better survival. The majority of our patients received a TBI-based MAC regimen, for which the most significant impact was demonstrated. Given the small number of patients who received a non–TBI-based conditioning regimen, we were unable to formally compare prognostic factors in TBI-versus non–TBI-based regimens. We also did not have specific TBI doses available to directly compare any potential impact that this might have had on outcomes. Interestingly, we found that the most significant impact of TBI was on survival in patients in CR2+, which seemed to be mediated primarily by better NRM. Patients without an HLA-identical sibling or matched unrelated donor experienced acceptable outcomes with alternative donors, albeit with a higher risk of NRM.

A recent study reported by Brammer et al. [6] found that the presence of minimal residual disease (MRD) at the time of HCT is highly predictive of relapse. Although we did not have information on MRD status at HCT, future studies will need to consider its impact on transplantation outcomes. Indeed, several recent studies have demonstrated the importance of achieving MRD in both B-ALL and T-ALL [7–10]. Gokbuget et al. [7], in a study of 580 patients with newly diagnosed ALL (34% with T-ALL), found significantly improved survival in those who achieved molecular negativity (80% versus 42%; $P = .0001$), with MRD as the sole significant variable for poor prognosis in multivariable analysis. Another recent study combined MRD assessment with mutational analysis to assess the prognosis in 423 patients with ALL (260 with B-ALL and 163 with T-ALL). A greater risk of relapse was seen in patients with T-ALL and MRD who did not have *NOTCH1/FBXW7* mutations or who harbored a *N/K-RAS* mutation and/or *PTEN* gene mutation [9]. Although the development of novel agents and molecular targets for T-ALL is lacking compared with those for B-ALL, the study of *NOTCH1* and other mutations may lead to the development of effective targeted therapies.

This study is limited by its multicenter retrospective nature. Our cohort was heterogeneous, and the choices of initial chemotherapy regimen, preparative regimen, TBI dosage, and transplant type were at the discretion of the treating physician. Notwithstanding the limitations of a retrospective cohort study, our analysis provides key clinically relevant information specific to this rare hematologic malignancy that can be used to counsel patients with high-risk T-ALL who are potential candidates for allogeneic HCT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflict of interest statement: There are no conflicts of interest to report.

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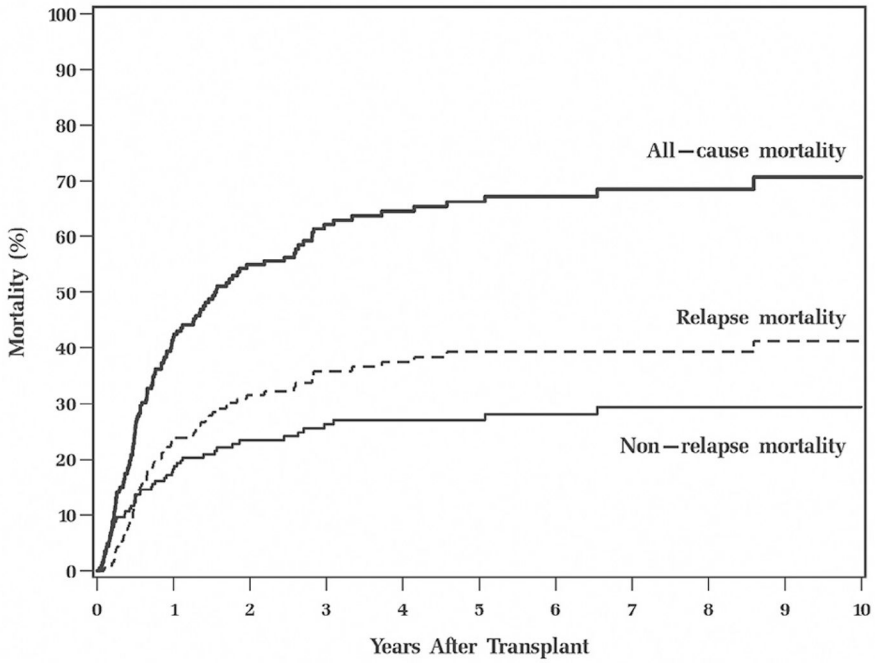

Figure 1.
Survival after allogeneic HCT for T-ALL.

Table 1

Patient, Disease, and Transplantation Characteristics

Characteristic	Value
No. of patients	208
Sex, n (%)	
Male	141 (68)
Female	67 (32)
Age at HCT, yr	
Median (range)	37 (17–72)
≤35, n (%)	91 (44)
>35, n (%)	117 (56)
Race/ethnicity, n (%)	
White	161 (78)
Black	15 (7)
Asian	15 (7)
Hispanic	12 (6)
Other	3 (1)
Missing	2
WBC count at diagnosis, $\times 10^9$/L	
Median (range)	21 (0.2–844)
<100, n (%)	146 (80)
≥100, n (%)	37 (20)
Missing, n	25
Bone marrow cytogenetics at diagnosis, n (%)	
Normal karyotype	69 (45)
Abnormal karyotype	84 (55)
Missing	55
CNS involvement at diagnosis, n (%)	
Yes	21 (12)
No	154 (88)
Missing	33
Previous chemotherapy regimens, n (%)	
1	74 (37)
2	85 (42)
≥3	43 (21)
Missing	6
Interval from diagnosis to HCT, mo, median (range)	9.0 (2.0–136.0)
Karnofsky Performance Status at HCT, n (%) (N = 181)	
90–100	123 (68)
≤80	58 (32)
Missing	27
HCT-CI score, n (%) (N = 177)	

Characteristic	Value
Low (0)	59 (33)
Intermediate (1–2)	65 (37)
High (≥3)	53 (30)
Missing	31
Disease status at transplantation, n (%)	
CR1	88 (43)
CR2 or greater	80 (39)
Relapsed/refractory	38 (18)
Missing	2
Conditioning regimen intensity, n (%)	
Myeloablative	174 (84)
Reduced-intensity/nonmyeloablative	34 (16)
Conditioning regimen, n (%)	
Cyclophosphamide/TBI	62 (30)
TBI/etoposide	45 (22)
Fludarabine/cyclophosphamide/TBI	25 (12)
Cyclophosphamide/TBI/thiotepa	14 (7)
Fludarabine/TBI	10 (5)
Cyclophosphamide/TBI/antithymocyte globulin	9 (4)
Busulfan/fludarabine	8 (4)
Fludarabine/melphalan	8 (4)
Other	27 (13)
Graft source, n (%)	
Peripheral blood stem cells	149 (72)
Bone marrow	35 (17)
Cord blood	24 (12)
Donor type, n (%)	
HLA-identical sibling	77 (37)
Matched unrelated	78 (38)
Mismatched unrelated	19 (9)
Umbilical cord blood	24 (12)
Haploidentical	10 (5)
CMV serostatus, n (%)	
Donor+/recipient+	55 (29)
Donor+/recipient−	23 (12)
Donor−/recipient+	54 (28)
Donor−/recipient−	59 (31)
Missing	17
GVHD prophylaxis, n (%)	
Calcineurin inhibitor + methotrexate	101 (49)
Calcineurin inhibitor + mycophenolate mofetil	36 (17)
Tacrolimus + sirolimus	20 (10)

Characteristic	Value
Post-transplantation cyclophosphamide	11 (5)
Ex vivo T cell depletion	15 (7)
In vivo T cell depletion	6 (3)
Other	10 (5)
Missing	1

Table 2

Post-Transplantation Outcomes for Allogeneic HCT to Treat T-ALL

Outcome	All Patients (n = 208)	Age, yr		Disease Status			Conditioning		TBI Conditioning		Donor Source		
		≤35 (n = 91)	>35 (n = 117)	CR1 (n = 88)	≥CR2 (n = 80)	Relapsed/ refractory (n = 38)	MAC (n = 174)	RIC (n = 34)	No TBI (n = 30)	TBI (n = 178)	Identical Sibling (n = 77)	MUD (n = 78)	Alternative Donor (n = 53)*
OS													
1 yr	58 (51–65)	62 (51–72)	55 (45–63)	64 (53–73)	58 (47–68)	46 (29–61)	60 (52–67)	48 (31–64)	36 (19–53)	62 (54–69)	58 (47–69)	61 (49–71)	53 (39–66)
5 yr	34 (27–41)	47 (36–58)	22 (14–32)	44 (32–55)	33 (22–45)	14 (5–29)	36 (28–44)	24 (10–41)	12 (2–29)	37 (29–45)	34 (23–45)	34 (21–47)	34 (20–49)
Relapse†													
1 yr	35 (29–42)	29 (20–39)	40 (31–49)	31 (22–41)	34 (24–45)	44 (27–59)	33 (26–41)	43 (26–60)	47 (28–64)	33 (26–40)	43 (32–54)	31 (21–42)	29 (17–42)
5 yr	42 (35–49)	34 (24–44)	49 (39–58)	38 (27–49)	38 (27–49)	60 (41–75)	41 (33–49)	47 (29–64)	47 (28–64)	41 (33–49)	52 (40–62)	38 (27–50)	31 (19–45)
Relapse mortality†													
1 yr	24 (18–30)	21 (13–30)	26 (19–35)	20 (12–29)	22 (13–31)	35 (20–51)	22 (16–29)	31 (16–47)	34 (17–52)	22 (16–29)	30 (20–40)	18 (11–28)	23 (12–35)
5 yr	39 (32–47)	28 (18–38)	49 (38–59)	32 (21–43)	38 (27–50)	56 (37–72)	38 (30–46)	43 (24–60)	42 (23–60)	39 (31–46)	47 (35–59)	38 (25–51)	28 (16–42)
NRM†													
1 yr	18 (13–24)	17 (10–26)	19 (12–27)	16 (9–25)	20 (12–30)	19 (8–33)	18 (12–24)	21 (9–36)	30 (15–47)	16 (11–22)	12 (6–20)	21 (13–31)	24 (13–36)
5 yr	27 (21–34)	25 (16–34)	29 (20–39)	25 (16–35)	29 (19–40)	29 (15–45)	26 (19–33)	33 (16–51)	46 (24–66)	24 (18–31)	19 (11–29)	29 (18–40)	38 (23–52)
Acute GVHD (grade I–IV)†													
3 mo	55 (48–61)	56 (45–66)	54 (44–62)	58 (47–68)	59 (48–69)	39 (24–55)	53 (45–60)	64 (44–78)	59 (38–74)	54 (47–61)	49 (38–60)	58 (47–69)	58 (43–70)
Chronic GVHD†													
1 yr	28 (22–34)	28 (19–38)	28 (20–36)	32 (23–43)	22 (13–32)	31 (16–47)	25 (19–32)	41 (23–57)	33 (17–51)	27 (20–34)	31 (21–41)	31 (20–41)	19 (9–31)

Data are outcome probability (%) with 95% CI. MUD indicates matched unrelated donor.

*Includes mismatched unrelated donor (n = 19), haploidentical donor with post-transplantation cyclophosphamide (n = 10), umbilical cord blood (n = 2 single unit; n = 22 double unit).

†Cumulative incidence estimates.