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CNS Involvement at Initial Diagnosis and Risk of Relapse After Allogeneic HCT for Acute Lymphoblastic Leukemia in First Complete Remission

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ABSTRACT

Outcomes of allogeneic hematopoietic cell transplantation (allo-HCT) for adult acute lymphoblastic leukemia (ALL) have improved over time. Studies have shown that total body irradiation (TBI) is the preferable type of myeloablative conditioning (MAC). However, outcomes based on central nervous system (CNS) involvement, namely CNS-positive versus CNS-negative, have not been compared. Here, we evaluated outcomes of 547 patients (CNS-positive = 96, CNS-negative = 451) who were allografted in the first complete remission (CR1) between 2009 and 2019. Primary endpoint was leukemia-free survival (LFS). Median follow-up was not different between the CNS-positive and CNS-negative groups (79 versus 67.2 months, $P = 0.58$). The CNS-positive group were younger (median age 31.3 versus 39.7 years, $P = 0.004$) and were allografted more recently (median year 2012 versus 2010, $P = 0.003$). In both groups, MAC was the preferred approach (82.3% versus 85.6%, $P = 0.41$). On multivariate analysis, the CNS-positive group had higher incidence of relapse (RI) (hazard ratio [HR] = 1.58 [95% confidence interval (CI) = 1.06-2.35], $P = 0.025$), but no adverse effect on LFS (HR = 1.38 [95% CI = 0.99-1.92], $P = 0.057$) or overall survival (OS) (HR = 1.28 [95% CI = 0.89-1.85], $P = 0.18$). A subgroup multivariate analysis limited to CNS-positive patients showed that a TBI-based MAC regimen resulted in better LFS (HR = 0.43 [95% CI = 0.22-0.83], $P = 0.01$) and OS (HR = 0.44 [95% CI = 0.21-0.92], $P = 0.03$) and lower RI (HR = 0.35 [95% CI = 0.15-0.79], $P = 0.01$). Another subgroup analysis in CNS-negative patients showed that MAC-TBI preparative regimens also showed a lower RI without a benefit in LFS or OS. While a MAC-TBI allo-HCT regimen may not be suitable to all, particularly for older patients with comorbidities, this approach should be considered for patients who are deemed fit and able to tolerate.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) represents 5% of adult lymphoid neoplasms.[1] While ALL represents a success story in children, treatment outcomes in adults lagged behind outcomes observed in the pediatric age group. Adoption of pediatric regimens for treatment of adult patients with ALL has translated into an improved survival predominantly in younger adults.[2] For instance, a prospective phase 2 study from the Cancer and Leukemia Group B (CALGB) known as CALGB 10403 evaluated a pediatric ALL regimen in young adults (age range 17–39 years) with newly diagnosed Philadelphia chromosome negative (Ph–) B-cell or with T-ALL.[2] CALGB 10403 showed a 3-year overall (OS) and disease-free (DFS) survival of 73% and 66%, respectively.[2] Additionally, The European Group for Research on Adult ALL (GRAALL) also evaluated pediatric regimens in adults with ALL up to 59 years of age.[3] The GRAALL-2005 study reported 5-year OS and event-free survival (EFS) rates of 58.5% and 52.2%, respectively.[3] Unfortunately, this survival benefit of pediatric regimens, in the GRAALL trial, was not apparent in adults older than 55 years, in whom the 5-year OS and EFS were reported at 27.4% and 25.8%, respectively.[3] The lack of benefit in patients older than 55 years of age was attributed to lower treatment compliance and poor treatment tolerability.[3] Results of GRAALL-2005 confirm the benefit of pediatric regimens in adult patients between 18 and 54 years of age.[3] Importantly, disease relapse remained a concern with reported 5-year cumulative incidence of relapse of 30.5% for all patients, and 39.1% for those older than 55 years of age.[3]

ALL represents the second most common indication for allogeneic hematopoietic cell transplantation (allo-HCT) in Europe.[4] Two published meta-analyses had shown the benefit of offering an allo-HCT for ALL in the first complete remission (CR1), particularly in patients younger than 35 years of age.[5,6] A study from the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) showed that outcomes of adults with ALL treated with an allo-HCT have improved over time; and that total body irradiation (TBI) should be considered as the preferable type of myeloablative conditioning (MAC).[7] Recently, a position paper on allo-HCT for adults with Ph– ALL in CR1 acknowledged its efficacy in this particular disease phenotype.[8] Yet, it questions the role of allo-HCT in adult patients who achieved a CR1 with a minimal residual disease negative status (MRD–) following pediatric-inspired intensified chemotherapy regimens.[8] In the case of adult patients with Ph+ ALL, offering an allo-HCT in CR1 continues to be considered the standard approach. However, a recently published multicenter, retrospective analysis did not show a benefit of allo-HCT in adults with Ph+ ALL who achieved a complete molecular remission within 90 days of treatment initiation.[9]

Specifically for ALL with central nervous system (CNS) involvement, there is a paucity of data on the efficacy of allo-HCT for this particular scenario. Yet, there is a clinical practice bias favoring use of myeloablative doses of TBI as part of the conditioning for patients allografted for ALL with CNS involvement despite the lack of randomized controlled studies. A single-institution study from City of Hope National Medical Center showed that patients with pre- allo-HCT CNS involvement had a higher risk of CNS relapse after transplantation (2-year CNS relapse: 9.6% versus 1.4%, $P < 0.0001$), inferior EFS (hazard ratio [HR], 1.52; $P = 0.003$), and worse OS (HR, 1.55; $P = 0.003$) vis-à-vis those allografted without CNS involvement.[10] The authors did not compare outcomes of the 2 groups when allografted in CR1.[10] Moreover, a recent observational nonrandomized comparative study from the Adult ALL Working Group of the Japan Society for Hematopoietic Cell Transplantation demonstrated that patients with CNS involvement had a higher incidence of relapse and an inferior OS.[11] Of note, in this analysis patients with CNS involvement were younger, had a worse disease status at time of allo-HCT, and a poorer pretransplant performance status.[11]

Here, we evaluated outcomes of patients with ALL with CNS involvement (CNS-positive) versus those without (CNS-negative)

Table 1

Patient-, Disease-, and Treatment-related Characteristics at Time of allo-HCT

Characteristics	CNS-negative (n = 451)	CNS-positive (n = 96)	*P*
Median (IQR) patient age, y	39.7 (28.3–49.3)	31.3 (23.6–44.5)	**0.004**
Patient gender, n (%)			0.21
Female	168 (37.3%)	42 (44.2%)	
Male	283 (62.7%)	53 (55.8%)	
Missing	–	1	
Donor gender, n (%)			**0.03**
Female	152 (33.9%)	44 (45.8%)	
Male	297 (66.1%)	52 (54.2%)	
Missing	2	–	
Median (range) year of allo-HCT	2010 (2009–2019)	2012 (2009–2019)	**0.003**
ALL types, n (%)			**0.01**
Ph– B-cell ALL	96 (21.3%)	27 (28.1%)	
Ph+ B-cell ALL	197 (43.7%)	26 (27.1%)	
T-cell	158 (35.0%)	43 (44.8%)	
Donor source, n (%)			0.52
MSD	196 (44.6%)	48 (51.1%)	
MUD	182 (41.5%	35 (37.2%)	
Mismatch UD	61 (13.9%)	11 (11.7%)	
UD (missing HLA info)	12	2	
Cell source, n (%)			**0.03**
BM	123 (27.3%)	37 (38.5%)	
PBSC	328 (72.7%)	59 (61.5%)	
Female donor to male recipient, n (%)			0.36
Yes	77 (17.1%)	20 (21.1%)	
No	373 (82.9%)	75 (78.9%)	
Missing	1	1	
KPS, n (%)			**0.02**
<90	77 (18.1%)	26 (29.2%)	
≥90	349 (81.9%)	63 (70.8%)	
Missing	25	7	
Conditioning regimen, n (%)			0.41
MAC	386 (85.6%)	79 (82.3%)	
RIC	65 (14.4%)	17 (17.7%)	
Radiation as part of conditioning, n (%)			0.82
No	113 (25.1%)	23 (24%)	
Yes	338 (74.9%)	73 (76%)	
Conditioning regimen (±TBI), n (%)			0.53
RIC-no TBI	45 (10;0%)	13 (13.5%)	
RIC-TBI	20 (4.4%)	4 (4.2%)	
MAC-no TBI	68 (15.1%)	10 (10.4%)	
MAC-TBI	318 (70.5%)	69 (71.9%)	
GVHD prophylaxis, n (%)			0.37
CSA +MTX	317 (70.6%)	62 (66.0%)	
Others	132 (29.4%)	32 (34.0%)	
Missing	2	2	
T-cell depletion, n (%)			0.14
Yes	239 (53.0%)	43 (44.8%)	
No	212 (47.0%)	53 (55.2%)	
Median (IQR) time from diagnosis to allo-HCT, mo	5.4 (4.5–6.9)	5.9 (4.9–6.8)	0.15

Bold denotes statistical significance.

ALL = acute lymphoblastic leukemia; allo-HCT = allogeneic hematopoietic cell transplantation; BM = bone marrow cells; CMV = cytomegalovirus; CR = complete remission; GVHD = graft-versus-host disease; IQR = interquartile range; KPS = Karnofsky performance score; MAC = myeloablative conditioning; MSD = HLA-matched sibling donor; MUD = HLA-matched unrelated donor; PBSC = peripheral blood stem cells; Ph = Philadelphia chromosome; Rel = relapse; RIC = reduced intensity conditioning; UD = unrelated donor.

Table 2

Univariate Analysis (All Study Population)

	LFS HR (95% CI) (*P*)	OS HR (95% CI) (*P*)	RI HR (95% CI) (*P*)	NRM HR (95% CI) (*P*)	GRFS HR (95% CI) (*P*	Grade 2–4 Acute GVHD HR (95% CI) (*P*)	Grade 3–4 Acute GVHD HR (95% CI) (*P*)	Chronic GVHD (All Grades) HR (95% CI) (*P*)	Chronic GVHD (Extensive) HR (95% CI) (*P*)
CNS involved (yes vs no)	1.20 (0.89-1.63) (0.24)	1.23 (0.88-1.72) (0.22)	1.27 (0.87-1.85) (0.22)	1.09 (0.66-1.82) (0.74)	1.01 (0.77-1.32) (0.94)	1.16 (0.81-1.65) (0.42)	0.85 (0.43-1.67) (0.64)	1.14 (0.82-1.61) (0.43)	0.94 (0.58-1.53) (0.82)
Patient's age (≥median vs <median)	**1.32 (1.04-1.68) (0.02)**	1.28 (0.98-1.66) (0.07)	1.32 (0.98-1.79) (0.07)	1.31 (0.89-1.94) (0.18)	1.22 (0.99-1.49) (0.065)	0.81 (0.61-1.07) (0.14)	0.66 (0.4-1.09) (0.11)	1.12 (0.86-1.45) (0.42)	1.17 (0.82-1.68) (0.38)
Year allo-HCT (≥median vs <median)	0.80 (0.62-1.04) (0.10)	0.84 (0.63-1.11) (0.22)	0.85 (0.61-1.19) (0.34)	0.73 (0.48-1.11) (0.14)	0.80 (0.64-1.00) (0.051)	1.09 (0.79-1.49) (0.60)	0.50 (0.31-0.83) (0.007)	0.87 (0.65-1.17) (0.36)	0.84 (0.57-1.24) (0.37)
Ph+ vs Ph–	**1.39 (1.01-1.92) (0.04)**	1.06 (0.75-1.52) (0.73)	1.49 (1.00-2.21) (0.052)	1.23 (0.71-2.13) (0.45)	1.26 (0.96-1.67) (0.10)	0.94 (0.66-1.36) (0.76)	1.50 (0.72-3.10) (0.28)	1.31 (0.93-1.86) (0.13	1.07 (0.67-1.71) (0.77)
T-cell vs Ph–	1.12 (0.80-1.57) (0.51)	1.13 (0.79-1.62) (0.50)	0.97 (0.63-1.49) (0.89)	1.39 (0.81-2.39) (0.23)	1.12 (0.84-1.49) (0.43)	0.93 (0.64-1.34) (0.69)	1.83 (0.89-3.75) (0.10)	1.17 (0.82-1.67) (0.39)	0.99 (0.62-1.60) (0.98)
URD vs MSD	0.84 (0.66-1.07) (0.17)	1.00 (0.77-1.31) (0.98)	**0.65 (0.48-0.88) (0.005)**	1.33 (0.89-2.00) (0.17)	0.93 (0.75-1.14) (0.46)	1.27 (0.96-1.69) (0.10)	1.14 (0.7-1.86) (0.61)	0.88 (0.68-1.15) (0.36)	0.93 (0.65-1.33) (0.69)
KPS (≥90 vs <90)	1.04 (0.76-1.43) (0.79)	0.91 (0.65-1.27) (0.59)	1.15 (0.76-1.73) (0.51)	0.90 (0.55-1.47) (0.66)	1.12 (0.85-1.47) (0.43)	0.89 (0.63-1.26) (0.51)	1.28 (0.65-2.52) (0.48)	0.91 (0.65-1.26) (0.57)	1.1(0.68-1.77) 1.2(0.70)
Patient gender Female vs male	0.90 (0.70-1.15) (0.39)	0.80 (0.61-1.06) (0.12)	0.92 (0.68-1.26) (0.62)	0.85 (0.56-1.29) (0.45)	0.82 (0.66-1.02) (0.07)	0.92 (0.69-1.23) (0.58)	0.59 (0.34-1.01) (0.056)	0.92 (0.70-1.21) (0.54)	0.86 (0.59-1.25) (0.42)
Donor gender Female vs male	0.96 (0.75-1.24) (0.77)	0.98 (0.75-1.29) (0.90)	1.01 (0.74-1.38) (0.96)	0.89 (0.59-1.35) (0.58)	1.03 (0.83-1.27) (0.80)	1.03 (0.77-1.38) (0.82)	0.96 (0.58-1.6) (0.88)	1.20 (0.92-1.58) (0.18)	1.00 (0.69-1.45) (1.00)
Female donor to male recipient (yes vs no)	1.03 (0.76-1.41) (0.83)	1.07 (0.76-1.5) (0.71)	1.04 (0.70-1.53) (0.86)	1.03 (0.62-1.71) (0.92)	1.16 (0.89-1.51) (0.27)	0.94 (0.65-1.36) (0.73)	1.06 (0.57-1.99) (0.85)	1.35 (0.97-1.87) (0.07)	1.32 (0.85-2.04) (0.22)
Patient CMV seropositive Yes vs no	1.10 (0.86-1.40) (0.45)	1.19 (0.91-1.55) (0.21)	1.01 (0.75-1.37) (0.93)	1.26 (0.84-1.90) (0.26)	1.14 (0.92-1.4) (0.23)	0.91 (0.69-1.20) (0.51)	0.91 (0.55-1.48) (0.70)	0.98 (0.75-1.28) (0.87)	1.08 (0.75-1.55) (0.69)
Donor CMV seropositive Yes vs no	1.14 (0.9-1.45) (0.28)	1.07 (0.82-1.4) (0.62)	1.05 (0.78-1.43) (0.74)	1.31 (0.88-1.95) (0.18)	1.10 (0.89-1.35) (0.38)	0.92 (0.69-1.22) (0.55)	0.82 (0.50-1.34) (0.43)	1.13 (0.87-1.48) (0.36)	1.12 (0.78-1.61) (0.53)
Regimen intensity RIC vs MAC	**1.69 (1.25-2.28) (0.0007)**	1.30 (0.92-1.84) (0.13)	**2.30 (1.62-3.26) (<0.0001)**	0.83 (0.45-1.56) (0.57)	**1.32 (1.01-1.73) (0.045)**	0.68 (0.44-1.06) (0.09)	0.37 (0.13-1.00) (0.051)	0.77 (0.50-1.17) (0.22)	0.74 (0.41-1.35) (0.33)
TBI as part of regimen Yes vs no	**0.61 (0.47-0.79) (0.0001)**	**0.67 (0.50-0.88) (0.005)**	**0.50 (0.37-0.69) (<0.0001)**	0.87 (0.55-1.37) (0.54)	**0.78 (0.62-0.98) (0.04)**	1.12 (0.80-1.56) (0.50)	**2.13 (1.05-4.30) (0.04)**	1.17 (0.85-1.62) (0.34)	1.07 (0.69-1.66) (0.75)
MAC-TBI vs all others	**0.60 (0.47-0.77) (<0.0001)**	**0.68 (0.52-0.89) (0.005)**	**0.46 (0.34-0.63) (<0.0001)**	0.97 (0.63-1.51) (0.90)	**0.77 (0.62-0.96) (0.02)**	1.21 (0.88-1.65) (0.25)	**2.10 (1.10-4.02) (0.03)**	1.20 (0.88-1.63) (0.25)	1.16 (0.76-1.76) (0.49)
T-cell depletion Yes vs no	1.12 (0.88-1.43) (0.34)	1.15 (0.88-1.49) (0.31)	1.16 (0.86-1.57) (0.34)	1.07 (0.72-1.58) (0.74)	0.86 (0.7-1.06) (0.15)	0.88 (0.67-1.16) (0.37)	**0.52 (0.32-0.86) (0.01)**	**0.63 (0.48-0.83) (0.0009)**	**0.51 (0.35-0.75) (0.0005)**
Donor source (PBSC vs BM)	1.16 (0.88-1.51) (0.29)	1.21 (0.9-1.63) (0.20)	0.94 (0.68-1.31) (0.73)	**1.72 (1.05-2.81) (0.03)**	**1.33 (1.05-1.69) (0.02)**	1.02 (0.75-1.38) (0.92)	1.18 (0.68-2.05) (0.56)	1.84 (1.33-2.55) (0.0002)	**1.70 (1.1-2.65) (0.02)**

Bold denotes statistical significance.

ALL = acute lymphoblastic leukemia; allo-HCT = allogeneic hematopoietic cell transplantation; BM = bone marrow cells; CI = confidence interval; CMV = cytomegalovirus; CNS = central nervous system; CR = complete remission; GRFS = composite end point of GVHD-free, relapse-free survival; GVHD = graft-versus-host disease; HR = hazard ratio; IQR = interquartile range; KPS = Karnofsky performance score; LFS = leukemia-free survival; MAC = myeloablative conditioning; MSD = HLA-matched sibling donor; MUD = HLA-matched unrelated donor; NRM = cumulative incidence of nonrelapse mortality; OS = overall survival; PBSC = peripheral blood stem cells; Ph = Philadelphia chromosome; Ph+ = Philadelphia positive; Rel = relapse; RI = cumulative incidence of relapse; RIC = reduced intensity conditioning; TBI = total body irradiation; UD = unrelated donor; URD = unrelated donor.

with remission status in CR1 when they received their first allo-HCT at an EBMT participating center.

METHODS

Study design and population

This is a retrospective observational study of patients who underwent an allo-HCT for ALL which was reported to the ALWP of EBMT. The EBMT is a voluntary working group of more than 600 transplant centers that are required to report all consecutive HCTs and follow-up once a year. This study was approved by the ALWP of the EBMT institutional review board and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. EBMT centers commit to obtain informed consent according to the local regulations applicable at the time of transplantation to report pseudonymized data to the EBMT.

Patients were eligible for inclusion in this study if they were of the adult age group (defined as ≥18 years) and received an allo-HCT for treatment of ALL in CR1 using a MAC or reduced intensity (RIC) conditioning regimen between 2009 and 2019. There was no preset upper age limit.

Data on patient-, disease-, and treatment-related characteristics collected at the time of allo-HCT are shown on Table 1. A total of 547 patients with ALL with CNS-positive (n = 96) or CNS-negative (n = 451) involvement receiving an allo-HCT at one of the EBMT participating centers were included. Completeness of follow-up after allo-HCT was calculated using the method described by Clark et al[12]; and they were 90% and 93% at the date of the analysis (June 01, 2021).

Statistical analysis

Patient-, disease-, and treatment-related characteristics at time of allo-HCT were compared using the X^2 test for categorical variables or the Mann–Whitney test for continuous parameters. Baseline characteristics were summarized using median, range, and/or interquartile range (IQR) for continuous variables, and frequency and percentage for categorical data. The reverse Kaplan–Meier method was used for estimation of follow-up.

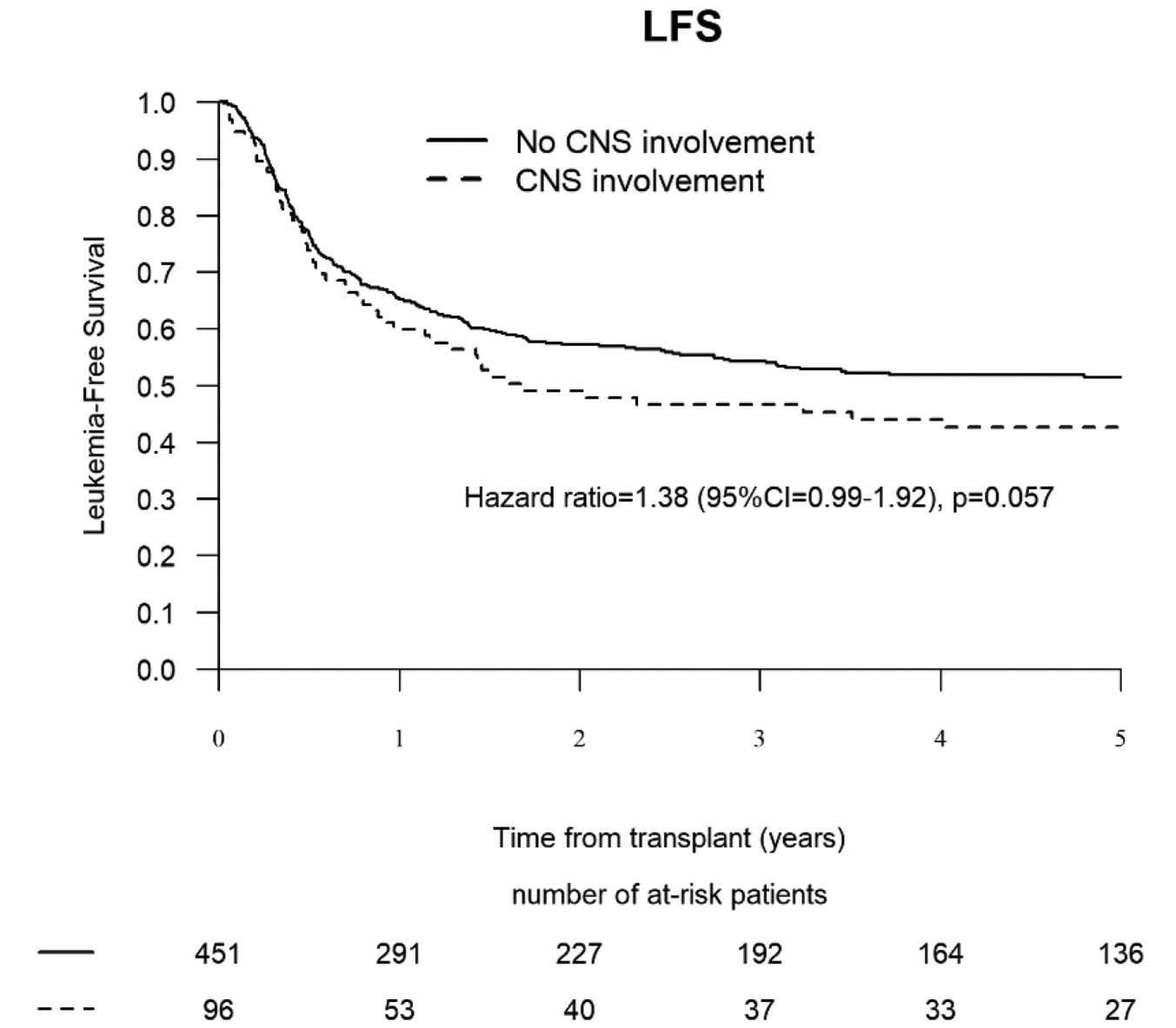

Figure 1. Leukemia-free survival. LFS = leukemia-free survival.

The primary endpoint was leukemia-free survival (LFS). Secondary endpoints included OS, cumulative incidences of relapse (RI), nonrelapse mortality (NRM), acute graft-versus-host disease GVHD (grades 2–4), acute GVHD (grades 3–4), chronic GVHD (any grade), chronic GVHD (extensive), and the composite end point of GVHD-free, relapse-free survival (GFRS). In addition, subgroup prognostic analyses limited to patients in the CNS-positive and CNS-negative were also performed.

Definitions

CR represents complete hematologic remission. LFS was defined as survival without evidence of relapse or progression. OS was defined as time from intervention (allo-HCT) to death, regardless of the cause. RI was defined as leukemia recurrence at any site. NRM was defined as death without evidence of relapse or progression. The intensity of the preparative regimen was categorized based on established definitions.[13] Whenever applicable, non-myeloablative conditioning regimens were included under the broader RIC category. Performance status was graded using the Karnofsky performance score (KPS).

Statistical Methods

All surviving patients were censored at the time of last contact on record. Probabilities of LFS and OS were calculated using the Kaplan–Meier method. All transplant-related deaths were competing events when studying relapse-related deaths. Cumulative incidence was used to estimate the end points of RI, NRM, acute GVHD, and chronic GVHD to accommodate for competing risks.[14] When assessing cumulative incidence of acute GVHD (day +180) and chronic GVHD (2–year), relapse and death were competing events.

Both univariate and multivariate analyses were performed using the Cox proportional-hazards regression model. We included in multivariate analyses variables with unbalanced distribution between the 2 groups and variables which are known to potentially influence posttransplant outcomes. Continuous variables were categorized according to the median for univariate analyses and included without categorization in the Cox proportional-hazards regression model. Patients with missing information were excluded from analyses.

For prognostic analysis specifically pertaining to the CNS-positive group, a stepwise selection was performed for

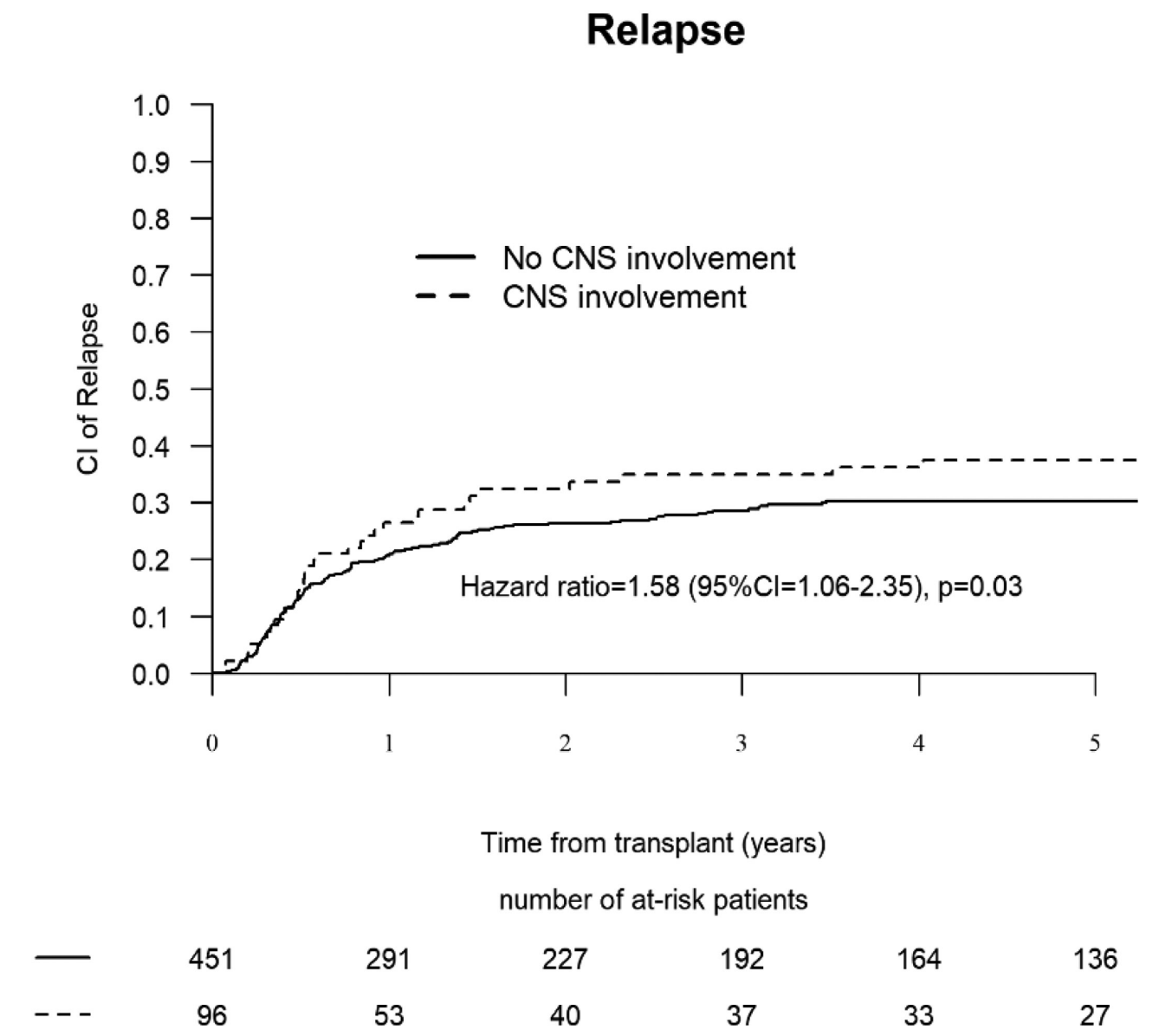

Figure 2. Cumulative incidence of relapse. CNS = central nervous system.

Table 3

Multivariate Analysis (All Study Population)

	LFS HR (95% CI) (*P*)	OS HR (95% CI) (*P*)	RI HR (95% CI) (*P*)	NRM HR (95% CI) (*P*)	GRFS HR (95% CI) (*P*)	Grade 2-4 acute GVHD HR (95% CI) (*P*)	Grade 3-4 acute GVHD HR (95% CI) (*P*)	Chronic GVHD (all grades) HR (95% CI) (*P*)	Chronic GVHD (extensive) HR (95% CI) (*P*)
CNS involved (yes vs no)	1.38 (0.99-1.92) (0.057)	1.28 (0.89-1.85) (0.18)	**1.58 (1.06-2.35) (0.03)**	1.05 (0.58-1.91) (0.86)	1.11 (0.82-1.48) (0.51)	1.27 (0.84-1.92) (0.26)	1.01 (0.48-2.12) (0.98)	1.17 (0.81-1.69) (0.41)	1.06 (0.6-1.87) (0.84)
Age (per 10 year)	1.10 (0.98-1.23) (0.11)	**1.16 (1.02-1.31) (0.02)**	1.03 (0.89-1.19) (0.72)	**1.24 (1.03-1.5) (0.03)**	1.08 (0.98-1.20) (0.13)	0.96 (0.84-1.09) (0.51)	1.05 (0.83-1.33) (0.68)	1.08 (0.95-1.23) (0.23)	1.16 (0.96-1.39) (0.12)
Year allo-HCT (recent vs distant)	**0.90 (0.84-0.95) (0.0006)**	**0.89 (0.83-0.95) (0.001)**	**0.90 (0.84-0.98) (0.01)**	**0.88 (0.79-0.98) (0.02)**	0.96 (0.92-1.01) (0.16)	0.99 (0.92-1.07) (0.83)	0.89 (0.79-1.02) (0.09)	1.00 (0.95-1.07) (0.87)	1.00 (0.91-1.09) (0.93)
Ph+ phenotype	1.09 (0.83-1.45) (0.53)	0.77 (0.57-1.05) (0.10)	1.3 (0.91-1.85) (0.15)	0.80 (0.50-1.28) (0.35)	1.08 (0.85-1.38) (0.52)	1.00 (0.71-1.40) (1.0)	0.99 (0.56-1.75) (0.96)	1.16 (0.85-1.56) (0.35)	1.02 (0.66-1.59) (0.93)
URD vs MSD	**0.73 (0.55-0.98) (0.04)**	0.94 (0.69-1.29) (0.71)	**0.51 (0.35-0.73) (0.0003)**	1.38 (0.84-2.25) (0.20)	1.02 (0.79-1.31) (0.90)	1.68 (1.17-2.41) (0.005)	**2.10 (1.17-3.76) (0.01)**	1.09 (0.79-1.51) (0.59)	1.41 (0.89-2.23) (0.14)
Female donor to male recipient (yes vs no)	1.08 (0.78-1.50) (0.64)	1.07 (0.75-1.53) (0.70)	1.12 (0.74-1.69) (0.59)	(0.59-1.73) (0.97)	1.18 (0.89-1.56) (0.25)	1.06 (0.72-1.57) (0.75)	1.08 (0.57-2.06) (0.81)	1.29 (0.91-1.81) (0.15)	1.20 (0.74-1.94) (0.47)
KPS ≥90 vs <90	1.15 (0.83-1.59) (0.41)	0.97 (0.69-1.38) (0.88)	1.25 (0.82-1.91) (0.29)	(0.61-1.7) (0.95)	1.22 (0.92-1.62) (0.16)	1.05 (0.71-1.53) (0.82)	1.55 (0.76-3.16) (0.22)	1.02 (0.73-1.45) (0.89)	1.21 (0.72-2.04) (0.47)
PBSC vs BM	0.99 (0.74-1.34) (0.97)	1.06 (0.76-1.47) (0.73)	0.75 (0.52-1.07) (0.11)	**1.74 (1.01-2.99) (0.047)**	**1.36 (1.04-1.76) (0.02)**	1.39 (0.96-2.03) (0.08)	1.68 (0.91-3.11) (0.10)	**2.13 (1.49-3.03) (<0.0001)**	**2.00 (1.20-3.36) (0.008)**
MAC-TBI vs others	**0.65 (0.48-0.88) (0.005)**	0.75 (0.54-1.04) (0.09)	**0.46 (0.32-0.66) (<0.0001)**	1.26 (0.73-2.17) (0.41)	0.84 (0.64-1.10) (0.21)	1.11 (0.74-1.65) (0.62)	1.79 (0.87-3.70) (0.12)	1.36 (0.94-1.95) (0.10)	1.29 (0.76-2.18) (0.34)
T-cell depletion (yes vs no)	1.33 (0.98-1.79) (0.07)	1.14 (0.82-1.58) (0.43)	**1.64 (1.13-2.4) (0.01)**	0.94 (0.57-1.53) (0.79)	0.82 (0.63-1.06) (0.13)	0.72 (0.49-1.06) (0.10)	**0.35 (0.19-0.65) (0.0009)**	**0.55 (0.39-0.78) (0.0007)**	**0.34 (0.2-0.57) (<0.0001)**

Bold denotes statistical significance.

ALL = acute lymphoblastic leukemia; allo-HCT = allogeneic hematopoietic cell transplantation; BM = bone marrow cells; CI = confidence interval; CMV = cytomegalovirus; CNS = central nervous system; CR = complete remission; GRFS = composite end point of GVHD-free, relapse-free survival; GVHD = graft-versus-host disease; HR = hazard ratio; IQR = interquartile range; KPS = Karnofsky performance score; LFS = leukemia-free survival; MAC = myeloablative conditioning; MSD = HLA-matched sibling donor; MUD = HLA-matched unrelated donor; NRM = cumulative incidence of nonrelapse mortality; OS = overall survival; PBSC = peripheral blood stem cells; Ph = Philadelphia chromosome; Ph+ = Philadelphia positive; Rel = relapse; RI = cumulative incidence of relapse; RIC = reduced intensity conditioning; TBI = total body irradiation; UD = unrelated donor; URD = unrelated donor.

conditioning intensity, cells source and T-cell depletion. Results were reported as the HR with 95% confidence intervals (CIs). Type I error rate was fixed at 0.05 for determination of factors associated with time-to-event outcomes. All *P* values were 2-sided. Statistical analyses were performed with SPSS 24.0 (SPSS Inc, Chicago, IL) and R 3.4.0 (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

RESULTS

The median number of reported cases per center for the entire study population was 3 (range, 1–76) and for patients with CNS involvement was 1 (range, 1–8). All patients in both groups were reported to be in hematologic CR1 at the time of allo-HCT.

The median follow-up for the entire population was 69.0 (IQR = 43.6–107.9) months. The median follow-up for patients in the CNS-positive and CNS-negative groups were 79 (IQR = 53–101) months and 67.2 (IQR = 43–109) months, respectively (*P* = 0.58).

Median age for patients in the CNS-positive group was lower (31.3 [IQR = 23.6–44.5] years versus 39.7 [IQR = 28.3–49.3] years, *P* = 0.004); and was transplanted more recently: median year 2012 (range, 2009–2019) versus 2010 (range, 2009–2019), *P* = 0.003. The CNS-positive group comprised a higher proportion of patients with Philadelphia-negative (Ph–) B ALL (28.1% versus 21.3%) and with T-cell ALL (44.8% versus 35.0%), *P* = 0.01. A significantly higher proportion of patients in the CNS-positive group had a KPS <90 (29.2% versus 18.1%, *P* = 0.02). The CNS-positive and CNS-negative groups were comparable with respect to patient gender (male, 55.8% versus 62.7%, *P* = 0.21), donor source (unrelated donor, 50.0% versus 56.5% *P* = 0.24) and intensity of the preparative regimen (MAC, 82.3% versus 85.6%, *P* = 0.41). These and other characteristics of the study populations are summarized in Table 1.

TBI dose

In the MAC group, the prescribed TBI dose were distributed as follows: 8 Gy (n = 10, 2.6%), 9 Gy (n = 18, 4.7%), 10 Gy (n = 4, 1.05%), 11 Gy (n = 4, 1.05%), 12 Gy (n = 331, 85.7%), 13 Gy (n = 6, 1.5%), 14 Gy (n = 11, 2.8%), and 16 Gy (n = 2, 0.6%).

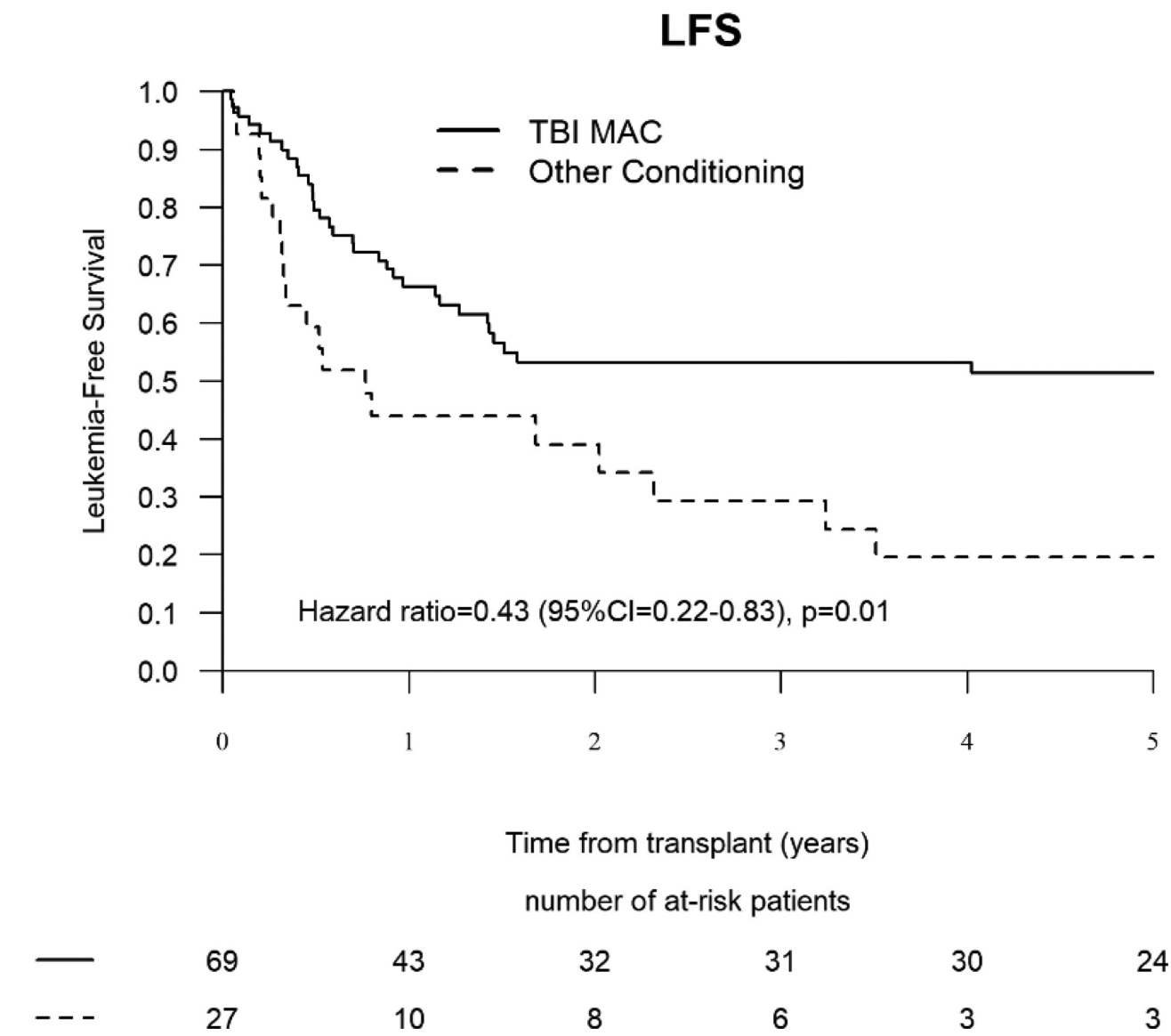

Figure 3. Leukemia-free survival. Multivariate analysis for patients with CNS involvement. CNS = central nervous system; LFS = leukemia-free survival; TBI-MAC = total body irradiation-myeloablative conditioning.

In the RIC group that received TBI as part of the preparative regimen, the prescribed TBI dose were as follows: 2 Gy (n = 17, 70.8%), 3 Gy (n = 1, 4.2%), and 6 Gy (n = 6, 25%).

Engraftment kinetics

The cumulative incidence of neutrophil engraftment at day +60 was 98.7% (95% CI = 96.9%-99.4%) and 94.7% (95% CI = 87.1%-97.9%) for the CNS-negative and the CNS-positive groups, respectively (P = 0.051). Graft failure was observed in 1.1% (n = 5/447, missing values in 4 cases) in the CNS-negative group and 4.2% (n = 4/95, missing values in 1 case) in the CNS-positive group (P = 0.055).

Univariate analysis

Presence of CNS involvement was not associated with worse LFS, OS, RI, or NRM (Table 2). Moreover, CNS involvement did not affect GRFS, grades 2–4 and grades 3–4 acute GVHD or chronic GVHD (all grades and extensive). Prescribing RIC regimens resulted in worse LFS. Use of MAC-TBI regimens resulted in better LFS, OS, and a lower RI (Table 2).

Multivariate analysis

CNS involvement was associated with a trend towards worse LFS (HR = 1.38 [95% CI = 0.99-1.92], P = 0.057) and a significantly higher RI (HR = 1.58 [95% CI = 1.06-2.35], P = 0.03 (Figures 1 and 2; Table 3). Older age was associated with inferior OS and worse NRM (Table 3). More recent allo-HCTs resulted in better LFS and OS and a lower RI and NRM. Use of unrelated donors (URD) versus matched sibling donors (MSD) resulted in better LFS, a lower RI and a significantly higher cumulative incidence of grade 3–4 acute GVHD (Table 3). Use of PBSC (versus BM) was associated with worse NRM and GRFS and a higher incidence of chronic GVHD (all grades and extensive) (Table 3). TBI-MAC resulted in better LFS and a lower RI (Table 3). T-cell depletion was independently associated with higher RI, a lower incidence of grade 3–4 acute GVHD and chronic GVHD (all grades and extensive), and a trend towards an inferior LFS (Table 3).

Subgroup analysis limited to patients with CNS involvement

In CNS-positive patients, the use of MAC-TBI preparative regimens resulted in a significantly improved LFS, OS and a lower RI (Figures 3–5; Table 4). Use of PBSC (versus BM) and

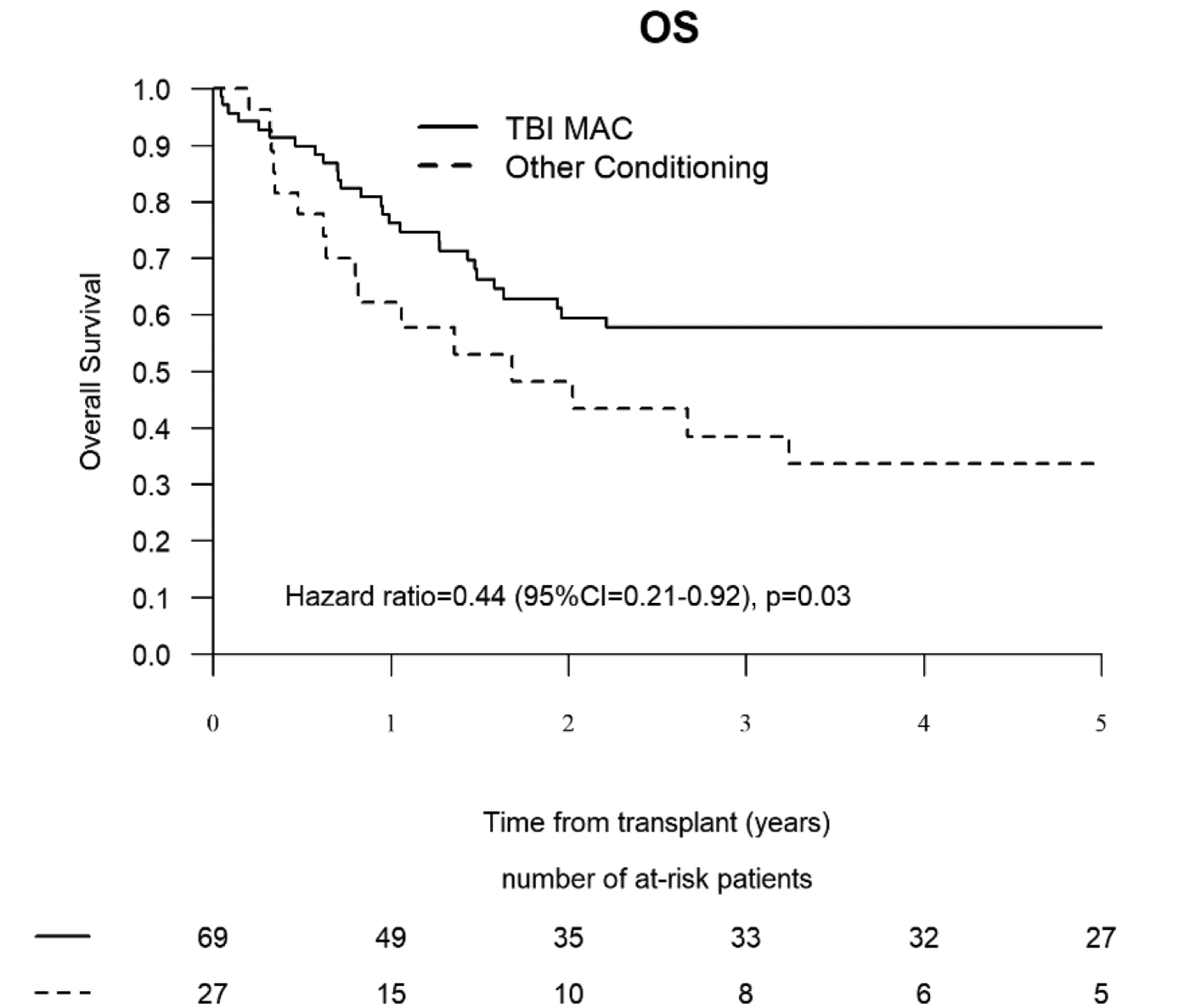

Figure 4. Overall survival. Multivariate analysis for patients with CNS involvement. CNS = central nervous system; OS = overall survival; TBI-MAC = total body irradiation-myeloablative conditioning.

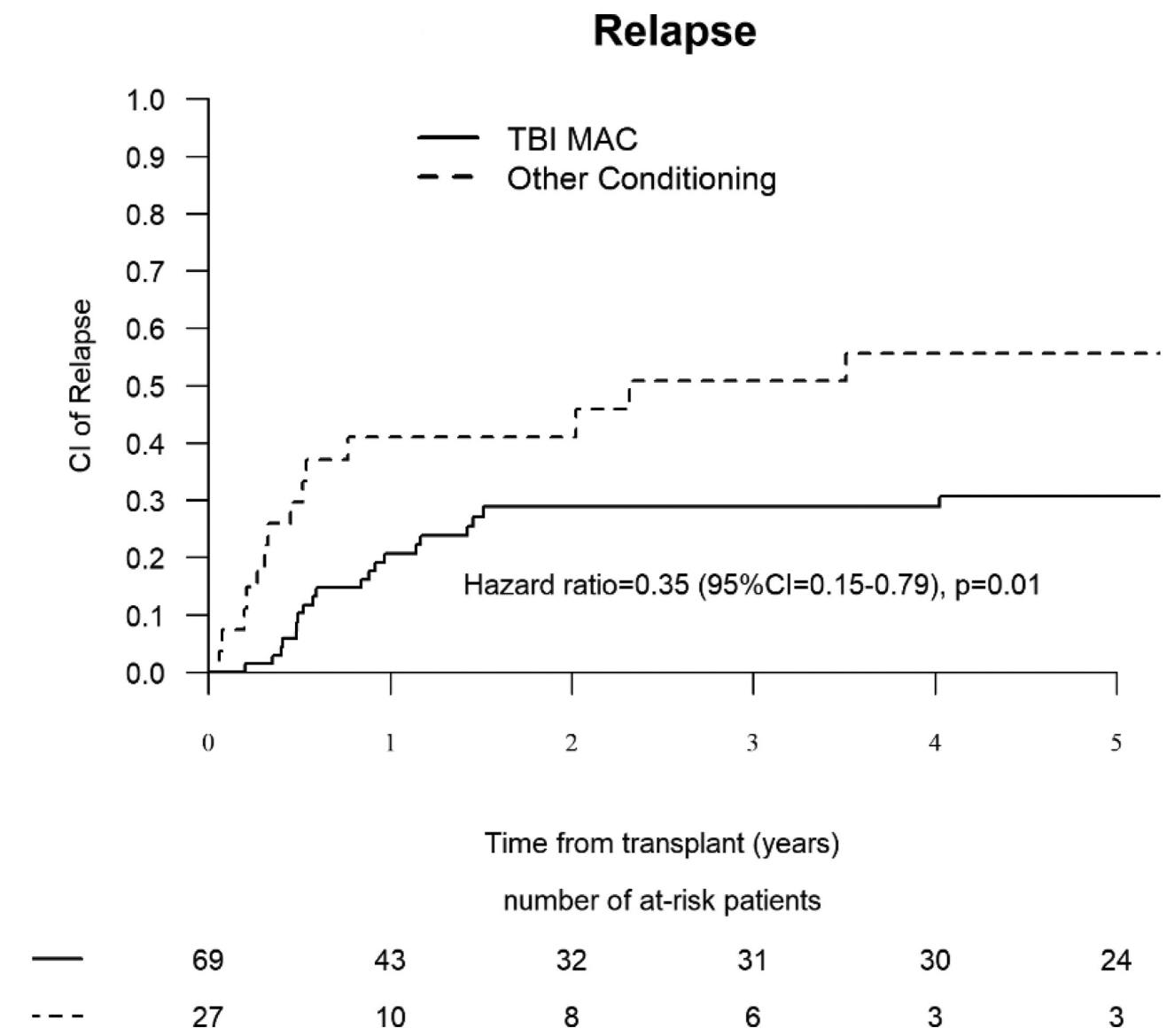

Figure 5. Cumulative incidence of relapse. Multivariate analysis for patients with CNS involvement. CNS = central nervous system; TBI-MAC = total body irradiation-myeloablative conditioning.

allo-HCTs performed more recently were also independently associated with better OS (Table 4). A Ph+ phenotype was an adverse prognostic indicator for lower GRFS (Table 4).

Subgroup analysis limited to patients without CNS involvement

A multivariate analysis in this population showed that use of MAC-TBI preparative regimens resulted in a lower RI, but at the expense of a higher NRM, ultimately not showing a benefit in LFS, OS, or GRFS. Use of URD resulted in a lower RI but a higher incidence of grade 2–4 and grade 3–4 acute GVHD. Use of PBSC (versus BM cells) was associated with a significantly higher NRM, worse GRFS and a higher incidence of grade 3–4 acute GVHD and chronic GVHD (both all grades and extensive). Use of T-cell depletion was associated with a higher RI and an inferior LFS (Suppl. Table S1).

DISCUSSION

This large observational study using registry data from the ALWP of the EBMT shows that CNS involvement at initial presentation remains an independent adverse prognostic factor for relapse in patients with ALL allografted in CR1, but it did not result in worse LFS or OS. This suggests that novel strategies after an allo-HCT ought to be studied within the context of a clinical trial. Such strategies include consolidation or maintenance with antileukemia agents able to cross the blood-brain barrier to help further reduce the risk of relapse. Older age (per increments of 10 years) and more distantly performed allo-HCT were independent predictors of inferior OS.

Use of MAC-TBI regimens was associated with better LFS and a significantly lower RI. The large majority of patients (90.6%) who were prescribed MAC-TBI received a dose ≥12 Gy. These findings are consistent with a previously published EBMT study which showed superior outcomes of TBI-based MAC regimens post allo-HCT for ALL.[7] Conversely, T-cell depletion had an adverse prognostic effect on relapse, a finding described in other studies,[15] emphasizing the relevant role of donor alloreactive T cells in facilitating a bona fide graft-versus-leukemia effect in ALL as is also the case in myeloid leukemias.[16–19] In our study, the use of URD (versus MSD) resulted in better LFS and a lower RI. The latter is consistent with recently published UKALL14 trial which used in vivo T-cell

Table 4

Multivariate Analysis (Limited to Patients With CNS Involvement)[a]

	LFS HR (95% CI) (*P*)	OS HR (95% CI) (*P*)	RI HR (95% CI) (*P*)	NRM HR (95% CI) (*P*)	GRFS HR (95% CI) (*P*)	Grade 2-4 Acute GVHD HR (95% CI) (*P*)	Chronic GVHD (all grades) HR (95% CI) (*P*)
Age (per 10 y)	0.94 (0.74-1.19) (0.59)	0.95 (0.71-1.25) (0.70)	(0.76-1.35) (0.92)	0.84 (0.55-1.26) (0.40)	1.05 (0.85-1.29) (0.67)	0.98 (0.76-1.26) (0.86)	1.08 (0.84-1.40) (0.54)
Year of allo-HCT (recent vs distant)	0.90 (0.79-1.03) (0.13)	**0.86 (0.74-0.99) (0.047)**	0.92 (0.78-1.08) (0.31)	0.88 (0.70-1.10) (0.27)	0.92 (0.81-1.03) (0.15)	0.97 (0.84-1.12) (0.70)	0.92 (0.79-1.06) (0.23)
Ph+ phenotype	1.25 (0.63-2.48) (0.52)	0.97 (0.42-2.24) (0.94)	0.86 (0.36-2.04) (0.73)	2.77 (0.98-7.82) (0.054)	**1.91 (1.05-3.48) (0.03)**	1.77 (0.86-3.65) (0.12)	1.15 (0.55-2.42) (0.71)
URD vs MSD	0.69 (0.39-1.23) (0.21)	0.87 (0.45-1.65) (0.66)	0.55 (0.27-1.13) (0.11)	1.10 (0.42-2.88) (0.84)	1.14 (0.68-1.91) (0.63)	1.44 (0.74-2.81) (0.29)	0.92 (0.49-1.73) (0.80)
PBSC vs BM	[b]	**0.53 (0.29-0.99) (0.046)**	[b]	[b]	[b]	[b]	[b]
MAC-TBI vs others	**0.43 (0.22-0.83) (0.01)**	**0.44 (0.21-0.92) (0.03)**	**0.35 (0.15-0.79) (0.01)**	[b]	[b]	[b]	[b]
T-cell depletion	[b]	[b]	[b]	[b]	[b]	[b]	[b]

Bold denotes statistical significance.

ALL = acute lymphoblastic leukemia; allo-HCT = allogeneic hematopoietic cell transplantation; BM = bone marrow cells; CI = confidence interval; CMV = cytomegalovirus; CNS = central nervous system; CR = complete remission; GRFS = composite end point of GVHD-free, relapse-free survival; GVHD = graft-versus-host disease; HR = hazard ratio; IQR = interquartile range; KPS = Karnofsky performance score; LFS = leukemia-free survival; MAC = myeloablative conditioning; MSD = HLA-matched sibling donor; MUD = HLA-matched unrelated donor; NRM = cumulative incidence of nonrelapse mortality; OS = overall survival; PBSC = peripheral blood stem cells; Ph = Philadelphia chromosome; Ph+ = Philadelphia positive; Rel = relapse; RI = cumulative incidence of relapse; RIC = reduced intensity conditioning; TBI = total body irradiation; UD = unrelated donor; URD = unrelated donor.

[a]Adjusted for age, year of allo-HCT, donor source (URD vs MSD), and Ph+ phenotype. Stepwise MAC-TBI, cell source (PBSC vs BM), and T-cell depletion.

[b]Variable removed from the model after stepwise selection.

depletion with alemtuzumab combined with fludarabine plus melphalan.[20]

When we performed a multivariate analysis limited to patients with CNS involvement, we again identified MAC-TBI regimens as an independent predictor of better LFS and OS and a lower RI. While the available data did not allow us to specifically assess the frequency of relapse according to site(s), we speculate that myeloablative doses of TBI might offer a therapeutic advantage at sanctuary sites known to be less responsive to conventional chemotherapy. Large prospective studies are needed to confirm this assumption. Furthermore, a separate subgroup analysis limited to patients without CNS involvement also demonstrated the benefit of TBI-based MAC regimens in reducing the incidence of relapse in this population without affecting LFS and OS, likely explained by the higher cumulative incidence of NRM (Suppl. Table S1). The UKALL14 trial reported a 4.2% incidence of CNS relapse at 4 years postallografting despite adding 8 doses of intrathecal therapy (IT) to a RIC regimen that combined fludarabine, melphalan and alemtuzumab.[20] The benefit (or lack thereof) of IT chemotherapy could not be ascertained because that intervention was not randomized.[20]

More recently performed allo-HCTs were associated with improved OS, LFS, and a lower NRM. We speculate that this benefit could be explained in part by the availability of better supportive therapies in more recent years. Interestingly, more recent allo-HCTs were also associated with a lower RI, a finding that appeared to be independent of other covariates included in the Cox model. Available data did not suggest a trend toward using higher TBI doses over time (data not shown).

We acknowledge several limitations of this study. First, due to the inherent nature of registry data, it was difficult to ascertain the true absence of CNS involvement in the CNS-negative group. All patients in both groups were reported by their respective transplant centers to be in CR at the time of the allograft, but there was no centralized review process to ascertain that patients indeed proceeded to an allo-HCT in CR. Moreover, data pertaining to prescribed CNS prophylaxis and/or treatment(s) of CNS disease prior to allo-HCT were not available to be incorporated in this analysis. Second, there were missing data on MRD status in both groups. In the CNS-negative group 165 (37%) of 451 patients did not have data available on MRD status. In the CNS-positive group 44 (46%) of 96 patients also did not have data on MRD status, hence limiting the statistical power to perform a comparison. Third, we were not able to determine if the purported benefit of TBI was related to a particular dose within a range of what is considered myeloablative. Fourth, we lacked specific data defining patterns of disease relapse, either in the CNS or systemically. Unfortunately, the specific site of relapse or the time when the relapse occurred are not routinely collected in the registry. Available data on relapse site were limited to either involving the BM or extramedullary involvement or both; this information was available in only 93 (55%) of 169 patients and was distributed as follows: BM involvement (n = 70/93, 75.3%), extramedullary (n = 16/93, 17.2%), or both (n = 7/93, 7.5%).

In the absence of a randomized clinical trial comparing MAC-TBI-versus MAC-non-TBI regimens for ALL with CNS involvement; and considering the unlikeliness that such a study be designed and conducted in the future, these results represent the best evidence favoring MAC-TBI regimens for patients with CNS-positive ALL in need of an allo-HCT. MAC-TBI regimens also appeared to confer a beneficial effect on lowering the RI in the CNS-negative group.

CONCLUSIONS

Notwithstanding all aforementioned limitations, our data support prescribing a MAC-TBI regimen for patients with ALL with CNS involvement at initial presentation whenever possible. Strategies to reduce relapse by incorporating novel therapies in the posttransplant consolidation/maintenance setting need to be studied within the context of a clinical trial as this continues to represent an area of unmet need.

AUTHOR CONTRIBUTIONS

MAK-D, AB and MM: designed the research study, analyzed the data, wrote the manuscript and approved the submission of the final version. ML: designed the research study, performed the statistical analysis, analyzed the data, wrote the manuscript, and approved the submission of the final version. US, SM, PC, MTR, MB, PP, A-LM, GS, AH, NS, ABR, JJC, IY-A, MA, SG, EB, ZP, and AN: contributed substantially to the research design, revised the paper critically, and approved the submission of the final version.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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