Biol Blood Marrow Transplant 26 (2020) 936–942

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Haploidentical

Haploidentical Transplantation with Post-Transplantation Cyclophosphamide for T Cell Acute Lymphoblastic Leukemia: A Report from the European Society for Blood and Marrow Transplantation Acute Leukemia Working Party

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Financial disclosure: See Acknowledgments on page 941.
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https://doi.org/10.1016/j.bbmt.2020.01.003

Article history:
Received 3 December 2019
Accepted 3 January 2020

Keywords:
Conditioning
Haploidentical stem cell transplantation
T-ALL
Thiotepa
Total body irradiation

A B S T R A C T

Allogeneic hematopoietic cell transplantation (HCT) is recommended in high-risk patients with T cell acute lymphoblastic leukemia (T-ALL). For patients without an HLA-identical donor, haploidentical (haplo-) HCT is becoming the leading source of stem cell donation. However, data are scarce on predictive factors for outcome in that setting. We identified 122 adults (20% female; median age, 31 years; range, 18 to 68 years) with T-ALL who underwent haplo-HCT with post-transplantation cyclophosphamide (ptCy) between 2010 and 2017. The median duration of follow-up of living patients was 23 months. The 2-year incidences of relapse and nonrelapse mortality were 45% and 21%, respectively. The 2-year leukemia-free survival (LFS), overall survival (OS), and graft-versus-host disease, relapse-free survival (GRFS) were 34%, 42%, and 27%, respectively. The 2-year LFS and OS were highly influenced by disease status at transplantation, being 49% and 55%, respectively, for patients in first complete remission (CR1); 34% and 50%, respectively, for those in second CR (CR2); and 8% and 12%, respectively, for patients with active disease. On multivariate analysis, only disease status was found to affect LFS and OS. Transplantation in CR2 negatively affected LFS, whereas active disease at the time of haplo-HCT negatively affected LFS and OS. In conclusion, haplo-HCT with ptCy produced encouraging results in this challenging disease, particularly when performed in patients in CR. Despite the limitation of the small sample size, our results were not affected by the type of conditioning, calling into question the need for total body irradiation-based myeloablative conditioning in that setting.

INTRODUCTION

T cell acute lymphoblastic leukemia (T-ALL) is a distinct malignant proliferation of precursor T cells and represents 20% to 25% of all ALL cases [1]. Clinically, T-ALL affects mainly young adults and often presents with mediastinal enlargement and central nervous system involvement in approximately 10% of cases [2]. Immunophenotyping allows classification of T-ALL into early T cell precursor (ETP), cortical, and mature subtypes, with ETP associated with a worse prognosis [2]. Karyotype complexity is associated with a poor prognosis, whereas improved outcomes have been reported in the presence of *NOTCH1* or *FBXW7* mutations [2-4].

The recent decade has witnessed a dramatic progress in the management of B cell ALL (B-ALL), including the use of rituximab, inotuzumab, blinatumomab, and CAR-T cells [5,6]. These new drugs have indeed revolutionized the management of B-ALL, including in the first-line setting for many of them. In comparison, little progress has been made in T-ALL. Nelarabine was granted accelerated approval by the US Food and Drug Administration in 2005 for patients with relapsed/refractory T-ALL [7]. Venetoclax is another promising option, particularly for patients with an ETP phenotype [8,9]. However, current treatment strategies still rely on classical ALL-type chemotherapy and the use of allogeneic hematopoietic cell transplantation (allo-HCT) in first complete remission (CR1) in the presence of either high-risk features [2] or minimal residual disease (MRD) positivity [10], as well as in patients in second complete remission (CR2) or beyond.

A donor versus no-donor comparison in 356 adults with T-ALL was carried out in a prospective trial by the Medical Research Council and the Eastern Cooperative Oncology Group (UKALL XII/ECOG 2993). The patients were treated uniformly between 1993 and 2006, and the trial demonstrated a significantly lower relapse incidence (RI) in patients with a matched sibling donor (MSD) compared with those without an MSD (25% versus 51% at 5 years; $P < .001$), which resulted in a higher 5-year overall survival (OS; 61% versus 46%; $P = .02$) [2].

For patients without an HLA-identical donor, haploidentical HCT (haplo-HCT) is becoming the leading stem cell donor source, particularly following the introduction of post-transplant cyclophosphamide (ptCy) [11]. However, data are scarce on haplo-HCT for T-ALL and on the predictive factors for transplantation outcomes in that setting, particularly with total body irradiation (TBI)-based myeloablative conditioning (MAC) being used less frequently. A recent multicenter retrospective cohort study included 208 adult patients with T-ALL who received an allo-HCT between 2000 and 2014 [12]. Overall, 37% of transplants were from an MSD, 38% were from a matched unrelated donor (MUD), and only 5% (10 patients) were from a haploidentical donor. After a median follow up of 38 months, the 5-year OS was 34% and RI was 41%.

The purpose of the present study was to assess the influences of patient, disease, and transplantation characteristics on outcomes after haplo-HCT with ptCy for T-ALL using a large sample from the European Society for Blood and Marrow Transplantation (EBMT) registry.

METHODS

Study Design and Data Collection

Data for this is a retrospective, registry-based multicenter analysis were provided and approved by the Acute Leukemia Working Party of the EBMT. The EBMT is a voluntary working group of more than 600 transplantation centers that are required to report all consecutive HCTs and follow-ups annually. Audits are routinely performed to determine the accuracy of the data. Since January 1, 2003, all transplantation centers have been required to obtain written informed consent before data registration with the EBMT, following the guidelines of the Helsinki Declaration of 1975. Eligibility criteria for this analysis included adult patients (age >18 years) with T-ALL who underwent haplo-HCT with ptCy between 2010 and 2017. The stem cell source was bone marrow (BM) or G-CSF-mobilized peripheral blood (PB). Patients who received in vivo T cell depletion with antithymocyte globulin or alemtuzumab were excluded.

Variables collected included recipient and donor age and sex, date of diagnosis, white blood cell (WBC) count and karyotype at diagnosis, time interval from diagnosis to transplantation, date of transplantation, previous auto-HCT, disease and MRD status at transplantation, Karnofsky Performance Status score at transplantation, and transplantation-related factors, including conditioning regimen, graft-versus-host disease (GVHD) prophylaxis, stem cell source (BM or PB), and patient and donor cytomegalovirus serostatus.

Definitions

MAC was defined as a regimen containing either TBI with a dose >6 Gy, a total dose of oral busulfan (Bu) >8 mg/kg, or a total i.v. Bu dose >6.4 mg/kg. All other regimens were defined as reduced-intensity conditioning (RIC) [13]. The diagnosis and grading of acute [14] and chronic GVHD [15] were performed by the transplantation centers using standard criteria.

Statistical Analysis

Endpoints included leukemia-free survival (LFS), OS, nonrelapse mortality (NRM), RI, acute and chronic GVHD, and GVHD-free, relapse-free survival (GRFS). All outcomes were measured from the time of haplo-HCT. LFS was defined as survival without leukemia relapse or progression; patients alive without leukemia relapse or progression were censored at the time of last contact. OS was defined as death from any cause. NRM was defined as death without previous leukemia relapse. GRFS was defined as events including

grade III-IV acute GVHD, extensive chronic GVHD, relapse, or death [16]. Surviving patients were censored at the time of last contact. The probabilities of OS and LFS were calculated using the Kaplan-Meier method. Cumulative incidence functions were used to estimate RI and NRM in a competing-risk setting. Death and relapse were considered competing events for acute and chronic GVHD.

For univariate analyses, continuous variables were categorized, and the median was used as a cutpoint. Univariate comparisons were performed using the log-rank test for LFS, OS, and GRFS and Gray's test for cumulative incidence. A Cox proportional hazards model was used for multivariate regression.

Multivariate results are expressed as hazard ratio (HR) with 95% confidence interval (CI). All tests were 2-sided. The type 1 error rate was fixed at .05 for determination of factors associated with time-to-event outcomes. All analyses were performed using SPSS 24.0 (IBM, Armonk, NY) and R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient and Transplantation Characteristics

Patient and transplantation characteristics are summarized in Tables 1 and 2. In total, 122 adults (20% female; median age 31 years; range 18 to 68 years) met the eligibility criteria for this study. The median WBC count at diagnosis was 33,500 K/L (interquartile range [IQR], 8000 to 82,000 K/L). Karyotype was normal in 37 patients, abnormal in 21, and missing in 64. Transplantation was performed in CR1 in 43% of the patients, in CR2 or beyond in 32%, and in active disease in 25%. Ten patients had undergone a previous auto-HCT. The Karnofsky Performance Scale score was <90% in 28 patients. Conditioning was TBI-based MAC in 28% of the patients, chemotherapy-based MAC in 53%, predominantly thiotepa/busulfan/fludarabine (TBF) in 40%, and RIC in 19%. The stem cell source was BM in 52% and PB in 48%, predominantly from male donors (57%). The median donor age was 42 years (range, 17 to 72 years). Most patients (76%) and donors (77%) were cytomegalovirus seropositive. Thirty-five percent of transplantations were a male recipient and a female donor. The median duration of follow-up of alive patients was 23 months (IQR, 12 to 38 months).

Transplantation Outcomes

Engraftment was successful in 95% of the patients. The cumulative incidence of acute GVHD grade II-IV and grade III-IV at day +100 was 22.5% and 13.5%, respectively, and the 2-year cumulative incidence of chronic and extensive chronic GVHD was 25.5% and 9.5%, respectively. The 2-year RI was 45%, and 2-year NRM was 21%. The 2-year LFS, OS, and GRFS were 34%, 42%, and 27%, respectively. A total of 61 patients died: 32 (53%) primarily from the original disease, 15 (25%) from infection, and 7 (12%) from GVHD. In the univariate analysis, the 2-year LFS and OS were highly influenced by disease status at transplantation (Figure 1A and B): 49% and 55%, respectively, for patients in CR1; 34% and 50%, respectively, for patients in CR2; and significantly worse, 8% and 12%, respectively, for patients with active disease ($P < .0001$ for both).

Table 1
Patient characteristics

Characteristics	Value
Patient age, yr, median (range)	31 (18-68)
Patient sex, n (%)	
Male	97 (80)
Female	24 (20)
WBC at diagnosis, G/L, median (range)	34 (.4-394)
Cytogenetics, n (%)	
Normal	37 (64)
Abnormal	21 (36)
Interval from diagnosis to transplant, mo, median (range)	10 (2-177)
Previous auto-HCT, n (%)	10 (8)
Patient CMV status, n (%)	
Negative	29 (24)
Positive	92 (76)

CMV indicates cytomegalovirus.

Table 2
Donor and Transplantation Characteristics

Characteristic	Value
Donor age, yr, median (range)	42 (17-72)
Donor sex, n (%)	
Male	70 (57)
Female	52 (43)
Female to male transplantation, n (%)	42 (35)
Donor CMV status, n (%)	
Negative	27 (23)
Positive	91 (77)
Year of transplantation, median (range)	2015 (2010-2017)
Status at transplantation, n (%)	
CR1	52 (43)
CR2	29 (24)
Advanced disease	41 (34)
MRD, n (%)	
Negative	22 (71)
Positive	9 (29)
Missing	60
Conditioning, n (%)	
MAC	99 (81)
TBI	34 (28)
No TBI	65 (53)
RIC	23 (19)

Multivariate Analysis

On multivariate analysis (Table 3), the use of PB stem cells significantly increased the risk of acute GVHD (HR, 4.63; $P = .004$), whereas the use of RIC reduced it (HR, .11; $P = .03$). Only disease status affected RI, LFS, OS, and GRFS (Tables 3 and 4). Transplantation in CR2 negatively affected RI (HR, 2.55; $P = .02$), LFS (HR, 2.09; $P = .02$), and GRFS (HR, 2.35; $P = .01$), whereas active disease at haplo-HCT negatively affected RI (HR, 4.56; $P = .0004$), LFS (HR, 3.88; $P < 10^{-4}$), OS (HR, 4.3; $P < 10^{-4}$), and GRFS (HR, 4.5; $P < 10^{-4}$). When multivariate analysis was restricted to patients who underwent transplantation in CR (Tables 5 and 6), the use of PB stem cells increased the risk of acute GVHD (HR, 3.5; $P = .04$), whereas only transplantation beyond CR1 affected LFS (HR, 1.91; $P = .045$), but not OS.

DISCUSSION

In this study, we evaluated the predictive factors for post-transplantation outcomes in T-ALL using a relatively large dataset of 122 patients from the EBMT. We found that LFS, OS, and GRFS were mostly affected by disease status, being significantly better in patients who underwent transplantation in CR1. The use of PB stem cells increased the risk of acute GVHD, whereas the use of RIC decreased it. Importantly, stem cell source and conditioning intensity had no influence on LFS, OS, or GRFS.

One important finding of this study is that outcomes were not affected by conditioning. In the setting of MSD or MUD allo-HCT for ALL, the optimal conditioning regimen remains unclear,

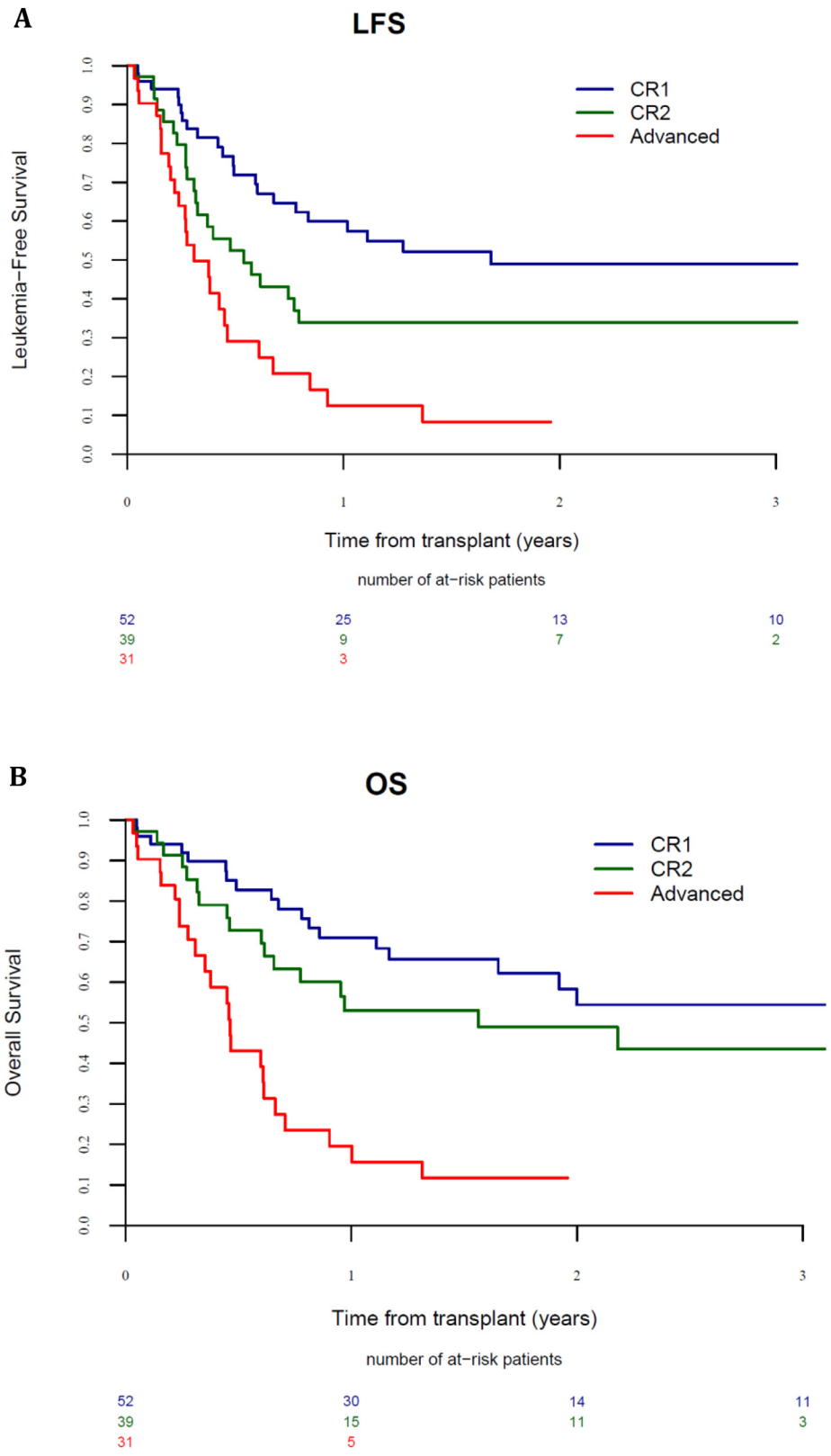

Figure 1. (A) LFS by disease status at transplantation. (B) OS by disease status at transplantation.

although multiple retrospective studies have favored TBI-based MAC [16-28], especially in young fit patients with T–ALL and in patients with refractory disease [27,29]. However, many of the studies favoring TBI were performed in the era of oral Bu. In a recent large EBMT study comprising 601 patients with T-ALL who underwent transplantation between 2000 and 2010, improved outcomes with TBI-based conditioning were observed in young patients (age <35 years) but not in older patients [27].

Table 3
Multivariate Analysis for Acute GVHD Grade II-IV, Chronic GVHD, and GRFS

Variable	Acute GVHD Grade II-IV, HR (95% CI) *P* Value	Chronic GVHD, HR (95% CI) *P* Value	GRFS, HR (95% CI) *P* Value
Patient age, per 10 yr	.87 (.58-1.33) .52	.84 (.57-1.26) .41	.82 (.64-1.05) .12
Status at HCT			
CR1 (reference)	1	1	1
CR2	2.38 (.83-6.87) .11	1.27 (.44-3.64) .66	**2.35 (1.2-4.61) .01**
Active disease	2.22 (.66-7.42) .20	1 (.28-3.64) .99	**4.5 (2.17-9.33) $<10^{-4}$**
KPS score ≥90	.97 (.33-2.85) .96	.43 (.15-1.17) .10	1.13 (.58-2.21) .72
PB vs BM	**4.63 (1.63-13.2) .004**	.99 (.37-2.7) .99	1.02 (.52-2.01) .94
RIC vs MAC	**.11 (.01-.82) .03**	.74 (.19-2.84) .66	.67 (.32-1.41) .29

KPS indicates Karnofsky Performance Status.

Table 4
Multivariate Analysis for Relapse, NRM, LFS, and OS

Variable	Relapse, HR (95% CI) *P* Value	NRM, HR (95% CI) *P* Value	LFS, HR (95% CI) *P* Value	OS, HR (95% CI) *P* Value
Patient age, per 10 yr	.78 (.58-1.05) .10	.92 (.61-1.37) .68	.83 (.66-1.04) .11	.89 (.69-1.13) .33
Status at HCT				
CR1 (reference)	1	1	1	1
CR2	**2.55 (1.18-5.53) .02**	1.32 (.41-4.29) .64	**2.09 (1.11-3.92) .02**	1.57 (.79-3.14) .2
Active disease	**4.56 (1.97-10.6) .0004**	3.14 (.99-9.98) .05	**3.88 (1.99-7.56) <10-4**	**4.3 (2.12-8.72) <10-4**
KPS score ≥90	.97 (.48-1.99) .94	.72 (.26-2.04) .54	.89 (.50-1.56) .67	.74 (.40-1.34) .32
PB vs BM	.76 (.4-1.47) .42	.55 (.20-1.47) .23	.71 (.42-1.2) .20	.77 (.43-1.36) .37
RIC vs MAC	1.24 (.54-2.82) .61	1.25 (.4-3.93) .70	1.32 (.69-2.52) .41	1.62 (.82-3.22) .17
Center (frailty)	.94	.24	.93	.94

Table 5
Multivariate Analysis for Acute GVHD Grade II-IV, Chronic GVHD, and GRFS for Patients in CR

Variable	GRFS, HR (95% CI) *P* value	Acute GVHD Grade II-IV, HR (95% CI) *P* value	Chronic GVHD, HR (95% CI) *P* value	GRFS, HR (95% CI) *P* value
Patient age per 10 yr	1.06 (.8-1.3) .67	1.0 (.6-1.5) .84	.9 (.6-1.4) .59	1.1 (.8-1.4) .67
Status at HCT				
CR2 vs CR1	1.7 (.9-3.03) .10	2.4 (.8-7.3) .12	1.2 (.4-3.4) .75	1.7 (.9-3.0) .10
KPS score 90	1.5 (.7-3.3) .35	.6 (.1-2.4) .46	.8 (.3-2.7) .68	1.5 (.7-3.3) .35
PB vs BM	1.0 (.5-1.8) .93	**3.52 (1.0-11.9) .043**	.9 (.3-2.5) .77	1.0 (.5-1.8) .9
RIC vs MAC	1.0 (.5-2.2) .95	.2 (.02-1.3) .08	.9 (.2-3.5) .88	1.00 (.5-2.2) .95
Center (frailty)	.94	.28	.29	.94

Another recent retrospective study of 208 adult patients with T-ALL demonstrated improved OS with the use of TBI [12]. However, new TBI-free thiotepa-based conditioning regimens are emerging, with recent data suggesting their noninferiority to TBI-based regimens [28]. It is noteworthy that in the present study, TBF conditioning was used in 40% of patients, whereas TBI-based MAC was used in 28%. Overall, our results suggest that TBF might be considered as a possible standard conditioning in the setting of T-ALL with ptCy.

Another important finding of our study is the very strong influence of disease status at transplantation on survival outcomes, challenging the indication for haplo-HCT in the setting of T-ALL with active disease. Interestingly, a recent EBMT study reported a 2-year LFS of 23% for patients with refractory T-ALL undergoing allo-HCT with sequential conditioning [30].

Limitations of this study include its relatively limited size, retrospective nature, heterogeneity of patient and transplantation characteristics, small number of patients with CR2/active

Table 6
Multivariate Analysis for Relapse, NRM, LFS, and OS for Patients in CR

Variable	Relapse, HR (95% CI) *P* value	NRM, HR (95% CI) *P* value	LFS, HR (95% CI) *P* value	OS, HR (95% CI) *P* value
Patient age per 10 yr	.8 (.6-1.2) .29	1.3 (.9-2.1) .19	1.0 (.7-1.3) .93	1.04 (.8-1.4) .81
Status at HCT				
CR2 vs CR1	**2.5 (1.16-5.5)** **.020**	1.1 (.4-3.5) .87	**1.9 (1.0-3.6)** **.045**	1.5 (.8-3.0) .24
KPS score ≥90	1.1 (.4-3.1) .80	1.4 (.3-6.7) .67	1.21 (.5-2.8) .65	.924 (.4-2.2) .86
PB vs BM	.8 (.4-1.8) .62	.5 (.15-1.6) .23	.7 (.4-1.4) .32	.7 (.3-1.5) .32
RIC vs MAC	1.6 (.6-4.1) .32	1.5 (.4-5.9) .59	1.6 (.7-3.5) .23	2.05 (.8-4.8) .09
Center (frailty)	.9	.3	.9	.9

disease, lack of data on MRD status and central nervous system status at transplantation, and T-ALL subtype for many patients. Nevertheless, this is the largest series on the use of haplo-HCT with ptCy in the setting of T-ALL published to date.

In conclusion, haplo-HCT with ptCy produced encouraging results in this challenging disease, particularly when performed in CR. With the limitation of a small sample size, outcomes were not affected by the type of conditioning, calling into question the need for TBI-based MAC in this setting. These results need to be confirmed in a large prospective study.

ACKNOWLEDGMENTS

Financial disclosure: Emanuele Angelucci has received honoraria from Novartis and Celgene; has served on local advisory boards for Jazz Pharmaceuticals, Bluebird Bio, and Roche; and has participated in data monitoring committees for Celgene, Vertex Pharmaceuticals, and CRISPR Therapeutics.

Conflict of interest statement: The other authors have no conflicts of interest to report.

REFERENCES

1. Swerdlow S, Campo E, Harris NL, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 2008.
2. Marks DI, Paietta EM, Moorman AV, et al. T-cell acute lymphoblastic leukemia in adults: clinical features, immunophenotype, cytogenetics, and outcome from the large randomized prospective trial (UKALL XII/ECOG 2993). *Blood*. 2009;114:5136–5145.
3. Vitale A, Guarini A, Ariola C, et al. Adult T-cell acute lymphoblastic leukemia: biologic profile at presentation and correlation with response to induction treatment in patients enrolled in the GIMEMA LAL 0496 protocol. *Blood*. 2006;107:473–479.
4. Trinquand A, Tanguy-Schmidt A, Ben Abdelali R, et al. Toward a NOTCH1/FBXW7/RAS/PTEN-based oncogenetic risk classification of adult T-cell acute lymphoblastic leukemia: a Group for Research in Adult Acute Lymphoblastic Leukemia study. *J Clin Oncol*. 2013;31:4333–4342.
5. Rafei H, Kantarjian HM, Jabbour EJ. Targeted therapy paves the way for the cure of acute lymphoblastic leukaemia. *Br J Haematol*. 2020;188:207–223.
6. Maffini E, Saraceni F, Lanza F. Treatment of adult patients with relapsed/refractory B-cell Philadelphia-negative acute lymphoblastic leukemia. *Clin Hematol Int*. 2019;1:85–93.
7. Cohen MH, Johnson JR, Justice R, Pazdur R. FDA drug approval summary: nelarabine (Arranon) for the treatment of T-cell lymphoblastic leukemia/lymphoma. *Oncologist*. 2008;13:709–714.
8. Peirs S, Matthijssens F, Goossens S, et al. ABT-199 mediated inhibition of BCL-2 as a novel therapeutic strategy in T-cell acute lymphoblastic leukemia. *Blood*. 2014;124:3738–3747.
9. El-Cheikh J, Moukalled NM, El Darsa H, et al. Feasibility of the combination of venetoclax and asparaginase-based chemotherapy for adult patients with relapsed/refractory acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk*. 2018;18:e441–e444.
10. Dhédin N, Huynh A, Maury S, et al. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. *Blood*. 2015;125:2486–2496.
11. Salas MQ, Law AD, Lam W, et al. Safety and efficacy of haploidentical peripheral blood stem cell transplantation for myeloid malignancies using post-transplantation cyclophosphamide and anti-thymocyte globulin as graft-versus-host disease prophylaxis. *Clin Hematol Int*. 2019;1:105–113.
12. Hamilton BK, Rybicki L, Abounader D, et al. Allogeneic hematopoietic cell transplantation for adult T cell acute lymphoblastic leukemia. *Biol Blood Marrow Transplant*. 2017;23:1117–1121.
13. Chen YB, Li S, Lane AA, et al. Phase I trial of maintenance sorafenib after allogeneic hematopoietic stem cell transplantation for fms-like tyrosine kinase 3 internal tandem duplication acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2014;20:2042–2048.
14. Brunner AM, Li S, Fathi AT, et al. Haematopoietic cell transplantation with and without sorafenib maintenance for patients with FLT 3–ITD acute myeloid leukaemia in first complete remission. *Br J Haematol*. 2016;175:496–504.
15. Antar A, Kharfan-Dabaja MA, Mahfouz R, Bazarbachi A. Sorafenib maintenance appears safe and improves clinical outcomes in FLT3-ITD acute myeloid leukemia after allogeneic hematopoietic cell transplantation. *Clin Lymphoma Myeloma Leuk*. 2015;15:298–302.
16. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009;15:1628–1633.
17. Granados E, de La Cámara R, Madero L, et al. Hematopoietic cell transplantation in acute lymphoblastic leukemia: better long-term event-free survival with conditioning regimens containing total body irradiation. *Haematologica*. 2000;85:1060–1067.
18. Bunin N, Aplenc R, Kamani N, Shaw K, Cnaan A, Simms S. Randomized trial of busulfan vs total body irradiation containing conditioning regimens for children with acute lymphoblastic leukemia: a Pediatric Blood and Marrow Transplant Consortium study. *Bone Marrow Transplantation*. 2003;32:543–548.
19. Davies SM, Ramsay NK, Klein JP, et al. Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia. *J Clin Oncol*. 2000;18:340–347.
20. Eroglu C, Pala C, Kaynar L, et al. Comparison of total body irradiation plus cyclophosphamide with busulfan plus cyclophosphamide as conditioning regimens in patients with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplant. *Leuk Lymphoma*. 2013;54:2474–2479.
21. Giebel S, Labopin M, Socié G, et al. Improving results of allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia in first complete remission: an analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica*. 2017;102:139–149.
22. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation*. 1974;18:295–304.
23. Terwey TH, Vega-Ruiz A, Hemmati P, et al. NIH-defined graft-versus-host disease after reduced-intensity or myeloablative conditioning in patients with acute myeloid leukemia. *Leukemia*. 2012;26:536–542.
24. Ruggeri A, Labopin M, Ciceri F, Mohty M, Nagler A. Definition of GvHD-free, relapse-free survival for registry-based studies: an ALWP-EBMT analysis on patients with AML in remission. *Bone Marrow Transplant*. 2016;51:610–611.
25. Ringdén O, Boumendil A, Labopin M, et al. Outcome of allogeneic hematopoietic stem cell transplantation in patients age >69 years with acute myeloid leukemia: on behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2019;25:1975–1983.
26. Mitsuhashi K, Kako S, Shigematsu A, et al. Comparison of cyclophosphamide combined with total body irradiation, oral busulfan, or intravenous busulfan

for allogeneic hematopoietic cell transplantation in adults with acute lymphoblastic leukemia. *Biol Blood Marrow Transplant*. 2016;22:2194–2200.
27. Cahu X, Labopin M, Giebel S, et al. Impact of conditioning with TBI in adult patients with T-cell ALL who receive a myeloablative allogeneic stem cell transplantation: a report from the Acute Leukemia Working Party of EBMT. *Bone Marrow Transplant*. 2016;51:351–357.
28. Eder S, Canaani J, Beohou E, et al. Thiotepa–based conditioning versus total body irradiation as myeloablative conditioning prior to allogeneic stem cell transplantation for acute lymphoblastic leukemia: a matched–pair analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Am J Hematol*. 2017;92:997–1003.
29. Pavlů J, Labopin M, Niittyvuopio R, et al. Measurable residual disease at myeloablative allogeneic transplantation in adults with acute lymphoblastic leukemia: a retrospective registry study on 2780 patients from the Acute Leukemia Working Party of the EBMT. *J Hematol Oncol*. 2019;12:108.
30. Bazarbachi AH, Al Hamed R, Labopin M, et al. Allogeneic stem-cell transplantation with sequential conditioning in adult patients with refractory or relapsed acute lymphoblastic leukemia: a report from the EBMT Acute Leukemia Working Party. *Bone Marrow Transplant*. 2019. https://doi.org/10.1038/s41409-019-0702-2. [e-pub ahead of print]. Accessed October 27, 2019.