Biol Blood Marrow Transplant 24 (2018) 2265–2270

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Outcomes of Advanced Hodgkin Lymphoma after Umbilical Cord Blood Transplantation: A Eurocord and EBMT Lymphoma and Cellular Therapy & Immunobiology Working Party Study

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Article history:
Received 18 June 2018
Accepted 12 July 2018

Key Words:
Hodgkin lymphoma
Umbilical cord blood transplantation
Adult patients

A B S T R A C T

Allogeneic stem cell transplantation is an alternative for patients with relapsed or refractory Hodgkin lymphoma (HL), but only limited data on unrelated umbilical cord blood transplantation (UCBT) are available. We analyzed 131 adults with HL who underwent UCBT in European Society for Blood and Marrow Transplantation centers from 2003 to 2015. Disease status at UCBT was complete remission (CR) in 59 patients (47%), and almost all patients had received a previous autologous stem cell transplantation. The 4-year progression-free survival (PFS) and overall survival (OS) were 26% (95% confidence interval [CI], 19% to 34%) and 46% (95% CI, 37% to 55%), respectively. Relapse incidence was 44% (95% CI, 36% to 54%), and nonrelapse mortality (NRM) was 31% (95% CI, 23% to 40%) at 4 years. In multivariate analysis refractory/relapsed disease status at UCBT was associated with increased relapse incidence (hazard ratio [HR], 3.14 [95% CI, 1.41 to 7.00], $P = .005$) and NRM (HR, 3.61 [95% CI, 1.58 to 8.27], $P = .002$) and lower

Financial disclosure: See Acknowledgments on page 2269.
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https://doi.org/10.1016/j.bbmt.2018.07.019

PFS (HR, 3.45 [95% CI, 1.95 to 6.10], $P < .001$) and OS (HR, 3.10 [95% CI, 1.60 to 5.99], $P = .001$). Conditioning regimen with cyclophosphamide + fludarabine + 2 Gy total body irradiation (Cy+Flu+2GyTBI) was associated with decreased risk of NRM (HR, .26 [95% CI, .10 to .64], $P = .004$). Moreover, Cy+Flu+2GyTBI conditioning regimen was associated with a better OS (HR, .25 [95% CI, .12 to .50], $P < .001$) and PFS (HR, .51 [95% CI, .27 to .96], $P = .04$). UCBT is feasible in heavily pretreated patients with HL. The reduced-intensity conditioning regimen with Cy+Flu+2GyTBI is associated with a better OS and NRM. However, outcomes are poor in patients not in CR at UCBT.

INTRODUCTION

Patients with relapsed or primary refractory Hodgkin lymphoma (HL) have a dismal prognosis. Intensive chemotherapy followed by autologous stem cell transplantation (ASCT) lengthens progression-free survival (PFS). Nevertheless, up to 50% of patients will experience relapse or progression after this treatment [1].

Allogeneic stem cell transplantation (HSCT) represents a potentially curative approach for patients who fail ASCT, with some reports indicating 5-year overall survival (OS) ranging from 30% to 40% [2,3]. However, the role of HSCT is poorly defined, albeit the potential graft-versus-lymphoma effect reported [4]. Furthermore, HL treatment after ASCT is changing with the emerging use of new therapeutic agents [5-9]. Many patients cannot benefit from HSCT because they lack a suitable donor or because of poor performance status. To overcome this issue, significant changes in practice have occurred in the last few years. First, the use of alternative donors such as haploidentical family donors has extended the possibility of HSCT for patients who lack a matched donor [10,11], showing a strong graft-versus-tumor effect. Second, the advent of reduced-intensity conditioning (RIC) regimens, associated with a decrease in toxicity and nonrelapse mortality (NRM), has allowed transplantation in patients with poor performance status, which is often observed in advanced lymphoma [12-15].

The recent use of anti-CD30 monoclonal antibody and anti-programmed death 1 (anti-PD1) agents has dramatically improved treatment of patients with HL who relapse after ASCT or fail previous chemotherapy regimens [16-18]. New drugs could be used as a bridge to HSCT, allowing patients previously not fit for this procedure to become eligible when a response is achieved [19].

To date, limited studies exist on outcomes of patients with HL undergoing umbilical cord blood transplantation (UCBT) [11,20].

Hereby, we describe outcomes of 131 patients with HL who underwent UCBT in Eurocord/European Society for Blood and Marrow Transplantation (EBMT) centers.

METHODS

Study Design and Inclusion Criteria

This is a retrospective registry-based study using Eurocord/EBMT data. Patients aged over 18 years and diagnosed with HL who received single or double UCBT as first allogeneic HSCT in EBMT centers between 2003 and 2015 were included. Patients who received manipulated cord blood or UCBT associated with other stem cell sources were excluded.

All patients or legal guardians gave informed consent for research. The study was conducted in accordance with the Declaration of Helsinki. The Internal Review Board of Eurocord/EBMT approved this study.

Endpoints and Definitions

The primary endpoint was PFS, defined as time from UCBT to relapse, progression, or death from any cause, whichever occurred first. Secondary endpoints were neutrophil engraftment, acute and chronic graft-versus-host disease (GVHD), NRM, relapse incidence (RI), and OS. Neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count $\geq .5 \times 10^9$/L, without evidence of autologous reconstitution. OS was defined as time from UCBT to death from any cause. Patients alive at last contact or lost to follow-up were censored. RI and NRM were defined as time from UCBT to relapse and to death without relapse, respectively.

A myeloablative conditioning (MAC) regimen was defined as a regimen containing total body irradiation (TBI) with a dose > 6 Gy, a dose of >8 mg/kg oral, >6.4 mg/kg i.v. busulfan, or containing >10 mg/kg thiotepa. Acute and chronic GVHD were evaluated based on standard criteria [21]. The probabilities of PFS and OS were estimated using the Kaplan-Meier method and compared with the log-rank test. Death without an event was treated as a competing risk to calculate probabilities of neutrophil engraftment and acute and chronic GVHD. Death without progression or relapse was considered as competing risk for RI. Relapse was the competing event for NRM.

A $P < .05$ was considered statistically significant. All variables found to have $P < .10$ in the univariate analysis were included in multivariate Cox models. Type I error was settled at .05. Confidence intervals (CIs) were estimated at 95%. Analyses were performed with SPSS 19 (version 19.0; IBM SPSS Statistics for Windows, Armonk, NY) and R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) software packages.

RESULTS

Table 1 describes patient characteristics. Most patients (n = 92, 84%) had nodular sclerosis classic histology. Karnofsky performance status was ≥90% in 83 patients (76%). Disease status at UCBT was complete remission (CR) in 59 patients (47%). Of the 54 patients with available data on the number of CR, 14 patients were in first CR, 16 were in second CR, and 24 in third CR.

One hundred twelve patients had a previous ASCT, including 19 patients who received 2 previous ASCTs. The median time from diagnosis to UCBT was 36 months (range, 8 to 295).

Information on treatment received before UCBT was available for 66 patients. Among these, 31 had Ann Arbor stages III

Table 1
Characteristics of Patients (N = 131)

Characteristics	Value
Median age at transplantation, yr (range)	29 (18-65)
Median time from diagnosis to UCBT, mo (range)	36 (8-295)
Histologic subtype	
Classic, nodular sclerosis	92 (84)
Classic, mixed cellularity	10 (10)
Classic, lymphocyte depletion	2 (2)
Nodular lymphocyte predominant lymphoma	4 (4)
Missing, n = 23	
Recipient CMV serology	
Negative	56 (44)
Positive	72 (56)
Missing, n = 3	
Gender	
Male	79 (60)
Female	52 (40)
Previous ASCT	
No	1 (1)
1	93 (82)
2	19 (17)
Missing, n = 18	
Median time from ASCT to UCBT, mo (range)	16 (2-280)
Disease status at transplantation	
CR	59 (47)
PR	34 (27)
Relapse/refractory	32 (26)
Missing, n = 6	
Median follow-up, mo (range)	55 (4-105)

Values are n (%) unless otherwise defined. CMV indicates cytomegalovirus; PR, partial remission.

to IV at diagnosis and 19 patients had Ann Arbor stages III to IV at UCBT. Patients received a median of 4 previous chemotherapy lines (range, 2 to 8), including ASCT. Anti-CD30 or anti-PD1 was part of the treatment received before UCBT for 22 patients, and 38 underwent radiotherapy before UCBT. After UCBT 15 patients received anti-CD30 or anti-PD1.

Table 2 shows transplant characteristics. The median number of total nucleated cells at cryopreservation was 4.08 $\times$ 10^7/kg (range, 1.45 to 11.43) for the overall cohort, 3.5 $\times$ 10^7/kg (range, 1.45 to 6.93) for single UCBT and 4.88 $\times$ 10^7/kg (range, 2.85 to 11.43) for double UCBT. Conditioning regimen consisted of RIC for 103 patients (78%), the most common being cyclophosphamide + fludarabine + low-dose (2 Gy) TBI (Cy+Flu+2GyTBI) (n = 71). Cyclosporine A + mycophenolate mofetil was used as GVHD prophylaxis in 85 patients (65%).

Engraftment and GVHD

One hundred seventeen patients engrafted in a median time of 18 days (range, 6 to 61). The cumulative incidence of neutrophil engraftment at 60 days was 88% (95% CI, 83% to 94%).

Thirty-three patients experienced grades II to IV acute GVHD in a median time of 28 days (range, 7 to 94). Fifteen patients had grades III to IV acute GVHD. The cumulative incidence of 100-day acute GVHD grades II to IV was 26% (95% CI, 20% to 35%).

Thirty-three patients developed chronic GVHD in a median time of 163 days (range, 76 to 935). Fourteen of them had extensive GVHD. The 4-year cumulative incidence of chronic GVHD was 32% (95% CI, 24% to 43%). In multivariate analysis double UCBT was the only factor significantly associated with a higher risk of aGVHD (HR, 2.89 [95% CI, 1.14 to 7.36], P = .03). None of the variables tested had a significant impact on chronic GVHD or engraftment.

Table 2
Transplant Characteristics

Characteristics	Value
Type of UCBT	
Single	66 (50)
Double	65 (50)
HLA mismatches	
0 to 1	31 (28)
2	80 (72)
Missing, n = 20	
Median TNC at cryopreservation, $\times 10^7$/kg (range)	4.08 (1.45-11.43)
Median year of UCBT (range)	2010 (2003-2015)
Conditioning regimen	
MAC	
Bu+Flu+Thio	18 (14)
Other	10 (8)
RIC	
Cy+Flu+TBI	71 (54)
Other	32 (24)
GVHD prophylaxis	
CsA + PDN	18 (14)
CsA + MMF	85 (65)
CsA	7 (5)
CsA + MTX	5 (4)
Other	16 (12)
Use of ATG or alemtuzumab	
Yes	49 (40)
No	74 (60)
Missing, n = 8	

Values are n (%) unless otherwise defined. TNC indicates total nucleated cell at collection; Bu, busulfan; CsA, cyclosporine A; PDN, prednisone, MMF, mycophenolate; MTX, methotrexate; ATG, antithymocyte globulin.

RI and NRM

The 4-year cumulative incidence of relapse was 44% (95% CI, 36% to 54%). Fifty-six patients relapsed after UCBT in a median time of 6 months (range, .4 to 84). The 4-year NRM was 31% (95% CI, 23% to 40%).

In multivariate analysis (Table 3) refractory/relapsed disease status at UCBT was associated with a higher risk of relapse (HR, 3.14 [95% CI, 1.41 to 7.00], P = .005) and NRM (HR, 3.61 [95% CI, 1.58 to 8.27], P = .002). Conditioning regimen with Cy +Flu+2GyTBI was associated with decreased risk of NRM (HR, .26 [95% CI, .10 to .64], P = .004).

Overall, 72 patients died: 31 from relapse, 39 from transplant-related causes (infection, n = 12; GVHD, n = 8; idiopathic pneumonia syndrome, n = 6; veno-occlusive disease, n = 2; PTLD (post-transplant lymphoproliferative disorder) Epstein-Barr virus, n = 2; cardiac toxicity, n = 1; multiorgan failure, n = 3; other causes, n = 5), and 2 from secondary malignancies.

PFS and OS

The median follow-up for survivors was 55 months (range, 4 to 105). The 4-year PFS and OS were 26% (95% CI, 19% to 34%) and 46% (95% CI, 37% to 55%), respectively (Figures 1 and 2). According to disease status at the time of UCBT, PFS and OS were 62% and 38% for patients in CR versus other disease status, respectively (Figures 3 and 4) (P < .001).

In multivariate analysis conditioning regimen with Cy+Flu +2GyTBI was associated with a better OS (HR, .25 [95% CI, .12 to .50], P < .001) and PFS (HR, .51 [95% CI, .27 to .96], P = .04). Also, refractory/relapsed disease status at UCBT was associated

Table 3
Multivariate Analysis

	HR	95% CI	P
RI			
Double vs. single UCBT	.98	.46-2.08	.95
Median year of UCBT > 2010 vs. ≤2010	1.31	.73-2.37	.37
Disease status at UCBT			
CR	ref		
PR	1.90	.95-3.80	.07
Relapsed/refractory	3.14	1.41-7.00	.005
Conditioning intensity (RIC vs. MAC)	.75	.29-1.95	.55
Cy+Flu+2GyTBI vs. other chemotherapy regimen	.98	.38-2.53	.97
NRM			
Double vs. single UCBT	1.20	.52-2.77	.67
Median year of UCBT > 2010 vs. ≤2010	.99	.50-1.97	.97
Disease status at UCBT			
CR	ref		
PR	1.20	.50-2.92	.69
Relapsed/refractory	3.61	1.58-8.28	.002
Conditioning intensity (RIC vs. MAC)	1.30	.57-2.98	.54
Cy+Flu+2GyTBI vs. other chemotherapy regimen	.26	.10-.64	.004
PFS			
Double vs. single UCBT	1.12	.63-1.97	.70
Median year of UCBT > 2010 vs. ≤2010	1.14	.73-1.79	.55
Disease status at UCBT			
CR	ref		
PR	1.57	.91-2.71	.10
Relapsed/refractory	3.45	1.95-6.10	<.001
Conditioning intensity (RIC vs. MAC)	1.04	.56-1.93	.91
Cy+Flu+2GyTBI vs. other chemotherapy regimen	.51	.27-.96	.04
OS			
Double vs. single UCBT	1.19	.64-2.24	.58
Median year of UCBT > 2010 vs. ≤2010	.90	.53-1.52	.68
Disease status at UCBT			
CR	ref		
PR	1.78	.94-3.34	.08
Relapsed/refractory	3.10	1.6-5.99	.001
Conditioning intensity (RIC vs. MAC)	1.22	.62-2.4	.56
Cy+Flu+2GyTBI vs. other chemotherapy regimen	.25	.12-.50	<.001

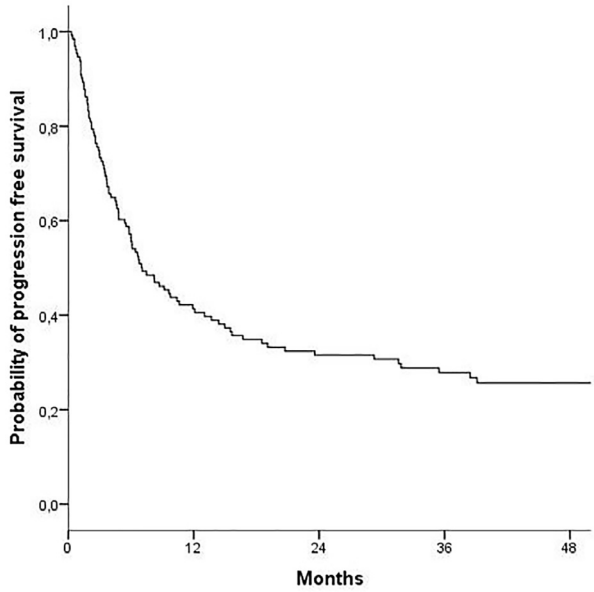

Figure 1. Four-year PFS (progression free survival) of the entire cohort .

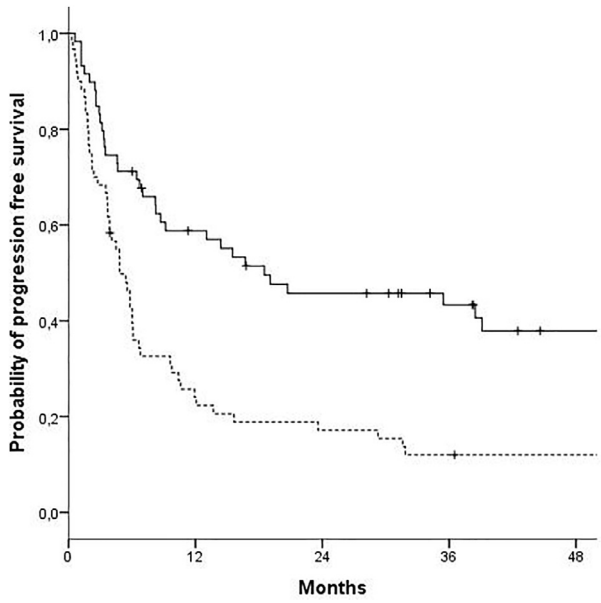

Figure 3. Four-year PFS according to disease status for patients in CR (*solid line*) and for patients in relapsed/refractory or partial remission (*dashed line*).

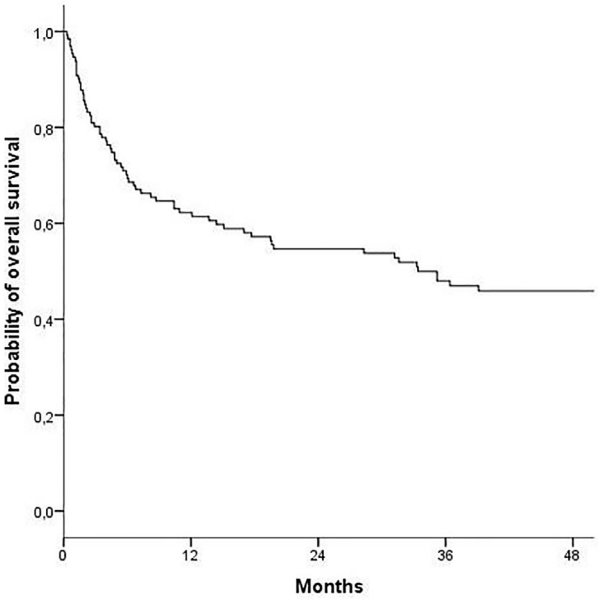

Figure 2. Four-year OS (overall survival) of the entire cohort**.**

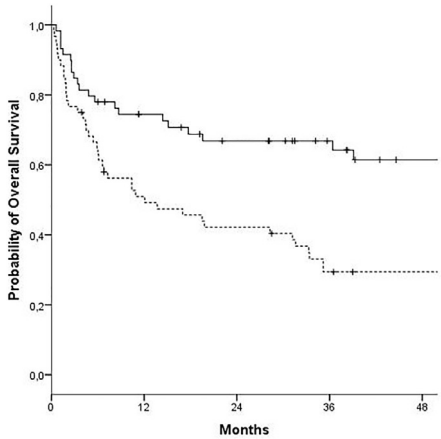

Figure 4. Four-year OS according to disease status for patients in CR (*solid line*) and for patients in relapsed/refractory or partial remission (*dashed line*).

with lower PFS (HR, 3.45 [95% CI, 1.95 to 6.10], $P < .001$) and OS (HR, 3.10 [95% CI, 1.60 to 5.99], $P = .001$).

DISCUSSION

This study reports 1 of the largest series of HL patients given UCBT. To date, there are limited studies in this settings, with few patients reported [20,22-26].

Brunstein et al. [20] described 65 patients with lymphoproliferative disease, 23 with HL, receiving UCBT with Cy+Flu+2Gy TBI as conditioning regimen. The 3-year PFS and OS for patients with HL were 33% and 43%, respectively, and the 3-year NRM was 13%. The Eurocord and EBMT Lymphoma Working Party reported a 1-year PFS of 40% and 1-year OS of 48% for adult patients with lymphoma (n = 104, 29 with HL) who underwent either RIC or MAC UCBT. For patients receiving RIC (n = 64), the conditioning regimen was Cy+Flu+2GyTBI in 42 cases. In this study patients who received low-dose TBI had better OS and PFS and lower NRM in the multivariate analysis [24]. Thompson et al. [26] showed the results of 27 patients with HL undergoing UCBT with RIC and MAC regimens, with a 5-year PFS, RI, and NRM of 31%, 38%, and 26%, respectively. Our results are in line with previous reports, supporting these findings in a more comprehensive and uniform cohort of patients who received UCBT.

Data on treatment before UCBT were available for 66 patients, with a median number of previous chemotherapy lines of 4 in this subgroup. Although we cannot attribute this result to the entire study cohort, this may indicate a tendency for a population composed of heavily treated patients who had at least 1 previous ASCT in almost all cases, which is consistent with the use of HSCT from alternative donors in this setting.

Our analysis showed that disease status at the time of UCBT is 1 of the most important factors impacting mortality, disease recurrence, PFS, and OS. The detrimental effect of disease status has been reported by Marcais et al. [22] in HL patients who

underwent HSCT from identical sibling or unrelated donors using bone marrow (n = 24), peripheral blood stem cells (n = 149), or cord blood (n = 17) as the stem cell source. Also, disease status at transplantation was the only risk factor associated with lower OS for 98 adult HL patients undergoing RIC HSCT from alternative donors (matched unrelated donor, n = 27; non–T cell–depleted haploidentical with post-transplant cyclophosphamide [HAPLO PTCy], n = 34; cord blood, n = 37) [11]. In this retrospective analysis, outcomes were not significantly different among recipients of cord blood, HAPLO PTCy, and matched unrelated donor in terms of RI, NRM, event-free survival, and OS [11]. These findings, together with our results, further support the importance of disease control before HSCT for HL patients, regardless of donor source.

We reported an NRM of 31% at 4 years, which is consistent with a heavily pretreated cohort of patients, some of whom (20%) transplanted after a MAC regimen. Similar results have been reported in other studies, including UCBT with RIC and MAC regimens [24-26]. In contrast, Brunstein et al. [20] and Gauthier et al. [11] reported lower rates of NRM (13% and 11%). This may be due to the inclusion of younger and less previously treated cohorts (almost all patients received less than 4 chemotherapy lines before HSCT) and of only RIC HSCT in both studies [11,20]. Importantly, we found a significant decrease in NRM for patients who received the Cy+Flu+2GyTBI (19% at 4 years) conditioning regimen. Furthermore, the results of the phase II study HDR-Allo trial with 92 advanced HL patients who underwent RIC HSCT corroborate our findings with an NRM of 17% at 2 years [15].

Previous reports demonstrated no difference in outcomes for advanced HL patients undergoing RIC using either UCBT (n = 9) or matched sibling donors (n = 12), although in a limited cohort [23]. More recently, Bachanova et al. [10] reported comparable outcomes in a large cohort of 1593 advanced lymphoma patients (346 with HL) transplanted with matched related donors, 7/8 mismatched unrelated, and cord blood. These results highlight the acceptable survival rate after alternative donor transplantation, extending the benefit of allogeneic transplant to patients with HL who lack an HLA-matched donor.

The use of other alternative donor transplants, such as HAPLO PTCy, is increasing over the years. Few studies have reported encouraging results for HAPLO PTCy in advanced HL with PFS ranging from 59% to 63% and OS from 63% to 77% [27,28]. More recently, HAPLO PTCy outcomes have been compared with HLA-identical sibling HSCT from 2 transplant centers, showing a reduced 3-year RI for HAPLO PTCy [29]. Also, in a limited cohort of patients with lymphoproliferative disease (HL = 9) who received more than 3 lines of prior treatment, combined CD34-selected haploidentical grafts with cord blood showed a PFS and OS of 73% and 86% at 1 year, respectively, supporting this treatment as a promising option [30].

The place of UCBT in the setting of relapsed/refractory HL should be carefully considered also in view of the increasing use of HAPLO PTCy transplant [31]. In the case of impossibility of donor lymphocyte infusion the use of new agents may be a suitable therapeutic option for patients with HL who relapse after UCBT. The use of novel agents has been recently explored in relapsed/refractory HL in association with bendamustine demonstrated to be a safety alternative to platinum-based chemotherapy before ASCT [32]. The possible application of this therapeutic option also as post-transplant maintenance should be evaluated further in clinical trials. New drugs could be used to improve response strength before UCBT or in maintenance after transplantation, as suggested for consolidation after ASCT per the AETHERA study [33]. In this randomized study anti-CD30 was used versus placebo after ASCT with a benefit in PFS.

Some reports have investigated the use of novel agents in the allogeneic setting [6,7,34]. Bazarbachi et al. [34] retrospectively compared outcomes of 210 patients who received anti-CD30 before HSCT to 218 patients who did not, and this was not associated with different outcomes between the 2 cohorts. Merryman et al. [35] reported 39 patients receiving anti-PD1 infusion before HSCT, with a higher than expected incidence of veno-occlusive disease (n = 3) and a 1-year cumulative incidence of grade IV acute GVHD of 13%.

More cases with longer follow-up are needed to better define the algorithm of UCBT for HL in view of new drugs currently available in clinical trials.

We are aware that some unmeasured factors may not have been considered, such as pretransplant-specific disease characteristics and anti-PD1 or CD30 use before or after UCBT that may have impacted our results. The inability to consider all factors is a common limitation in retrospective analyses. Nevertheless, our study remains of value because it is 1 of the largest reports describing UCBT in patients with HL.

In conclusion, UCBT is a feasible alternative for patients with HL. When considering this donor source, a RIC regimen with low-dose TBI has showed encouraging results and is effective in reducing toxicity and mortality. The use of novel agents, as both a bridge to transplant and maintenance treatment, needs to be further investigated in prospective clinical studies.

ACKNOWLEDGMENTS

The authors thanks the Centre Scientifique de Monaco and all the EBMT transplant centers that have included data in this study: France: Paris, Necker; Denmark: Copenhagen, Rigshospitalet; France: Paris, Saint-Louis; Spain: Barcelona, Hospital Clinic; Belgium: Brussels, Children`s University Hospital BMT Unit; United Kingdom: London Surrey Royal Marsden Hospital; Austria: Vienna, Medizinische Universitaet Wien; France: Marseille, Paoli Calmettes (adulte); France: Besançon, Saint Jacques; The Netherlands: Utrecht, University Medical Centre; Italy: Bologna, Bologna University, S. Orsola-Malpighi Hospital; United Kingdom: Glasgow, Gartnaval General Hospital; The Netherlands: Rotterdam, Erasmus MC-Daniel den Hoed Cancer Centre; France: Saint-Etienne, Hopital Nord / Institut de Cancérologie de la Loire, France: Caen, CHU de Caen; France: Créteil, Henri Mondor; France: Nantes, Hotel Dieu; United Kingdom: Leeds, Mid Yorkshire Hospitals NHS Trust; Spain: Barcelona, Hospital Santa Creu i Sant Pau; France: Paris, La Pitié; France: Bordeaux, Haut-Lévêque; France: Grenoble, Tronche CHU/Albert Michallon; France: Tours, Hopital Bretonneau, Service d`Oncologie Médicale; France: Clermont-Ferrand, Hotel Dieu CHU/Jean Perrin; Spain: Valencia, Hospital Clínico Universitario; Italy: Roma, Ospedale S. Camillo; Portugal: Porto, Inst. Portugues de Oncologia do Porto; Portugal: Lisboa, Inst. Portugues Oncologia; Italy: Firenze, Azienda Ospedaliero Universitaria Meyer: Ospedale di Careggi; Italy: Torino, Ospedale Infantile Regina Margherita Onco-Ematologia Pediatrica; Austria: Graz, Medical University Graz; Israel: Haifa, Rambam Medical Center; United Kingdom: Bristol, Royal Hospital for Children; United Kingdom: Birmingham, Queen Elizabeth Hospital; Italy: Palermo, Ospedale V. Cervello; Netherlands: Maastricht, University Hospital Maastricht Dept. Internal Med. Hematology /Oncology; Spain: Barcelona, Hospital Vall d Hebron; Italy: Cuneo, Az. Ospedaliera S. Croce e Carle; Turkey: Ankara, University Faculty of Medicine; France: Angers, CHR Angers, Italy: Bergamo, Ospedali Riuniti di Bergamo; France: Brest, Augustin Morvan; France: Rennes, Pontchaillou; Spain:

Valencia, Hospital Universitario La Fe, France: Lyon, Edouard Herriot (adulte), France: Nancy, Brabois; Italy: Palermo, Ospedale La Maddalena; Italy: Udine, University Hospital; United Kingdom: Nottingham, Nottingham City Hospital; Belgium: Liege, University of Liege; Spain: Salamanca, Hospital Clínico; Israel: Tel-Hashomer, Chaim Sheba Medical Center; Italy: Roma, Rome Transplant Network; United Kingdom: London, St. Bartholomew`s and The Royal London NHS Trust, Spain: Sevilla, Hospital Universitario Virgen del Rocío; France: Paris, Saint-Antoine; United Kingdom: Sheffield, Royal Hallamshire Hospital; Italy: Catania, Ospedale Ferrarotto; France: Paris, Hôpital St. Louis Service Hemato-oncologie (adulte); Italy: Milano, San Raffaele Scientific Institute, Turkey: Antalya, Medical Park Hospitals; France: Montpellier, Lapeyronie (adulte).

Financial disclosure: The authors have nothing to disclose.

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

Authorship statement: A.P., A.R., and E.G. designed the study. A.P., F.V., V.R., K.T.M., E.G., and A.R. wrote the manuscript. A.P. performed the statistical analysis. F.V. and C.K. helped with data verification. E.Ge., N.M., A.E., P.C., D.G., N.Mo., V.L., J.Y.C., D.B., M.A., T.Z., H.S., G.G., M.T.R., Y.B., L.L.C., A.N., J.S., Y.K., N.M., F.B., S.P.R., and S.M. provided cases for the study. All authors edited and approved the manuscript.

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