EBMT

ARTICLE

Outcomes of graft failure after umbilical cord blood transplantation in acute leukemia: a study from Eurocord and the Acute Leukemia Working Party of the EBMT

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Graft failure has remained a limitation of umbilical cord blood transplantation (CBT). Here, we assessed the outcomes of patients who experienced graft failure after CBT. Inclusion criteria were patients (age ≥ 18 years) experiencing graft failure after unrelated CBT (single or double) between 2005 and 2016, for acute myelogenous leukemia (AML) or acute lymphoblastic leukemia (ALL), no prior allogeneic or autologous transplantation, no other stem cell product. The study included 87 patients. At 1-year, cumulative incidence of relapse and nonrelapse mortality (NRM) was 35% and 37%, respectively. One-year overall survival (OS) and progression-free survival (PFS) was 40% and 29%, respectively. Forty-six patients underwent a salvage second transplantation with 1-year and 2-year OS and PFS from second transplantation 41% and 34% for OS, and 37% and 34% for PFS, respectively. In multivariate analysis, complete remission (CR) at CBT (HR = 0.45, 95% CI 0.25–0.83, $P = 0.01$) and reduced-intensity conditioning (HR = 0.51, 95% CI 0.29–0.91, $P = 0.023$) were associated with better OS. In conclusion, in this retrospective study, we observed that approximately one-quarter of patients experiencing graft failure after CBT remained alive without relapse 2 years later.

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INTRODUCTION

Umbilical cord blood transplantation (CBT) is a therapeutic option for acute leukemia (AL) patients who lack a human leukocyte antigen (HLA)-identical sibling donor [1–4]. Furthermore, recent studies have demonstrated favorable hematopoietic stem cell transplantation (HSCT) outcomes in AL patients with detectable measurable residual disease (MRD) at transplantation when offered a CBT [4, 5].

The main limitation of CBT in adults has been a higher incidence of graft failure in comparison to other transplant approaches (i.e. unrelated donor transplantation or HLA-haploidentical transplantation) [6]. Specifically, in the EBMT registry, the reported cumulative incidence of graft failure for AL patients receiving a single or double CBT has been around 12% [7, 8].

Previous studies have identified risk factors for graft failure after CBT. In patients with AL, these include nucleated cells $\leq 2.5 \times 10^7$/kg at cryopreservation, increasing HLA-disparities, and the presence of donor-specific anti-HLA antibodies [7, 9]. Importantly, a prior study from our group has shown that the probability of engraftment after CBT in patients without neutrophil engraftment at day 42 was only 5% [7]. Here, we describe the outcomes of patients who experienced graft failure (defined as non-engraftment without signs of leukemia recurrence at day 42) after CBT for AL. We then assessed which factors were associated with better outcomes in these patients.

PATIENTS AND METHODS

Patients

This current manuscript reports the results of a retrospective, multicenter analysis using the dataset of the Acute Leukemia Working Party (ALWP) of the European Society of Bone Marrow Transplantation (EBMT), and of the clinical research group Eurocord. The EBMT is a voluntary working group of more than 600 transplant centers that are required to report all consecutive stem cell transplantations and follow-ups once a year. The EBMT Med A/B standardized data collection forms are submitted to the registry by transplant center personnel following written informed consent from patients in accordance with center ethical research guidelines. Accuracy of data is assured by the individual transplant centers and by

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quality control measures such as regular internal and external audits. The results of disease assessments at HSCT were also submitted and form the basis of this report.

Inclusion criteria for the current study included unrelated CBT (single or double) between 2005 and 2016, adult (age ≥ 18 years), AML or ALL, no prior allogeneic or autologous transplantation, no other stem cell product. Graft failure was defined as non-engraftment without signs of leukemia recurrence at day 42. Data from all patients meeting the inclusion/exclusion criteria were included. Start time was date of transplant for all study endpoints.

Definitions

For the current analysis, graft failure was defined as absence of neutrophil engraftment at day 42 and no prior leukemia relapse. Neutrophil engraftment was defined as first of 3 consecutive days with a neutrophil count of at least 0.5×10^9/L as previously reported [10]. Relapse was defined as cytologic evidence of leukemia after transplantation. Non-relapse mortality (NRM) was defined as death without prior or current disease recurrence defined as evidence of cytologic AL relapse [11]. Reduced-intensity conditioning (RIC) was defined as regimens combining fludarabine with either < 6 Gy total body irradiation, ≤ 8 mg/kg busulfan, or ≤140 mg/m^2 melphalan or with other nonmyeloablative drugs [12]. HLA-compatibility included antigen level typing for HLA-A and -B and allele level typing for HLA-DRB1. CB units were mostly 4–6/6 HLA-A, -B and -DRB1 matched to the recipient and to the other unit in the case of double CBT.

Statistical methods

Patients were censored at the time of last follow-up. OS, and PFS were estimated using the Kaplan-Meier method. Cumulative incidence functions were used for relapse incidence and NRM in a competing risk setting, with death and relapse being considered as competing events. Cumulative incidence functions were also used to calculate second transplantation incidence, with relapse and death being considered as competing events. For all patients included in the study, the outcomes are given starting from the date of the first CBT (given the definition of graft failure in the current manuscript no events occurred before day 42 with the exception of second transplantation occurring before day 42 for the incidence of second transplantation endpoint). For analyses assessing outcomes after second allogeneic HSCT, the day 0 is the day of the second transplantation.

Multivariate analyses were performed for assessing factors impacting transplant outcomes using Cox cause-specific models.

All tests were two sided. The type I error rate was fixed at 0.05 for determination of factors associated with time to event outcomes. Statistical analyses were performed with R 3.4.3 (R Development Core Team, Vienna, Austria) software packages.

RESULTS

Patients

A total of 184 patients met the inclusion criteria and had no registered achievement of neutrophil engraftment. Among them, 82 patients died before day 42 and 14 patients relapsed before day 42 (1 patient had missing information on relapse) leaving a total of 87 patients meeting the definition of graft failure used in this study (i.e. absence of neutrophil engraftment at day 42 and no prior leukemia relapse). This included 65 patients with acute myeloid leukemia (AML) and 22 with ALL (Table 1). Sixty-three patients were in CR at transplantation while 23 were not and the data was missing for 1 patient. Forty patients (46%) received a RIC with the low-dose (<6 Gy) total body irradiation (TBI), cyclophosphamide, fludarabine (TCF) regimen, while the remaining 47 patients received a myeloablative conditioning (MAC) containing ($n = 20$) or not ($n = 27$) TBI. Forty-four patients received a single CBT while the remaining 43 received a double CBT. Among the 87 patients included in the study, chimerism information was unfortunately missing for 52 patients, 23 had recipient reconstitution, 9 were in complete aplasia and 3 had mixed chimerism.

Table 1. Patient characteristics.

Variable	Level	$n = 87$
Patient age (years)	Median (min-max) [IQR]	43.4 (18.1–66.7) [34.6–52.5]
Patient sex	Male	47 (54%)
	Female	40 (46%)
Karnofsky score	<80	6 (8%)
	≥80	69 (92%)
	missing	12
Intensity of conditioning	RIC	40 (46%)
	MAC	47 (54%)
ATG	Yes	42
	No	41
	Missing	4
Year of transplantation	Median (min-max) [IQR]	2010 (2005–2016) [2008–2012]
Cell source	CB	44 (51%)
	Double CB	43 (49%)
Total infused nucleated cells (10e7/kg)	Median (IQR)	3.9 (2.5–5.2)
	Missing	20
Total infused CD34 positive cells (10e5/kg)	Median (IQR)	1.3 (0.9–2.1)
	Missing	28
Number of HLA-mismatches (6 HLA loci)	Median (min-max) [IQR]	2 (0–4) [1,2]
	Missing	16

IQR interquartile range, *ATG* anti-thymocyte globulin, *RIC* reduced-intensity conditioning, *MAC* myeloablative conditioning, *CB* cord blood.

Outcomes in patients with graft failure after first CBT

The 3-month and 2-year cumulative incidences of relapse were 18% (95% CI 11–27%) and 39% (95% CI 29–50%), respectively. For NRM, the figures were 22% (95% CI 14–31%) and 38% (95% CI 28–48%), respectively. One and 2-year PFS were 29% (95% CI 21–40%) and 23% (95% CI 15–34%), respectively. One and 2-year OS were 40% (95% CI 31–52%) and 31% (95% CI 22–42%) (Fig. 1).

Causes of death were original disease ($n = 28$), infection ($n = 23$), GVHD ($n = 3$), multiple organ failure ($n = 2$), SOS ($n = 1$), hemorrhage ($n = 1$), secondary malignancy ($n = 1$), other ($n = 3$), and missing ($n = 3$).

Among the 87 patients with graft failure, 46 patients received a second allogeneic HSCT before relapse (Fig. 2) (see below). The 2-, and 3-month (from first CBT) cumulative incidence of second transplantation before relapse was 25%, and 43%, respectively. The criteria that led to the decision of performing or not a second allogeneic HSCT was unfortunately not collected in the registry.

In multivariate analysis, being in CR at CBT was associated with a trend for a lower relapse incidence (hazard ratio (HR) = 0.44, 95% CI 0.19–1.01, P = 0.053) and better PFS (HR = 0.58, 95% CI 0.32–1.05, $P = 0.073$) and significantly better OS (HR = 0.45, 95% CI 0.25–0.83, $P = 0.01$) (Table 2). A RIC regimen was associated with a lower incidence of NRM (HR = 0.26, 95% CI 0.1–0.65, $P = 0.004$) leading to better OS (HR = 0.51, 95% CI 0.29–0.91, $P = 0.023$) and a suggestion towards better PFS (HR = 0.63, 95% CI 0.36–1.1, $P = 0.1$).

Outcomes after second allogeneic HSCT for graft failure

A total of 46 patients reported to the registry, had received a salvage second transplantation before evidence of disease

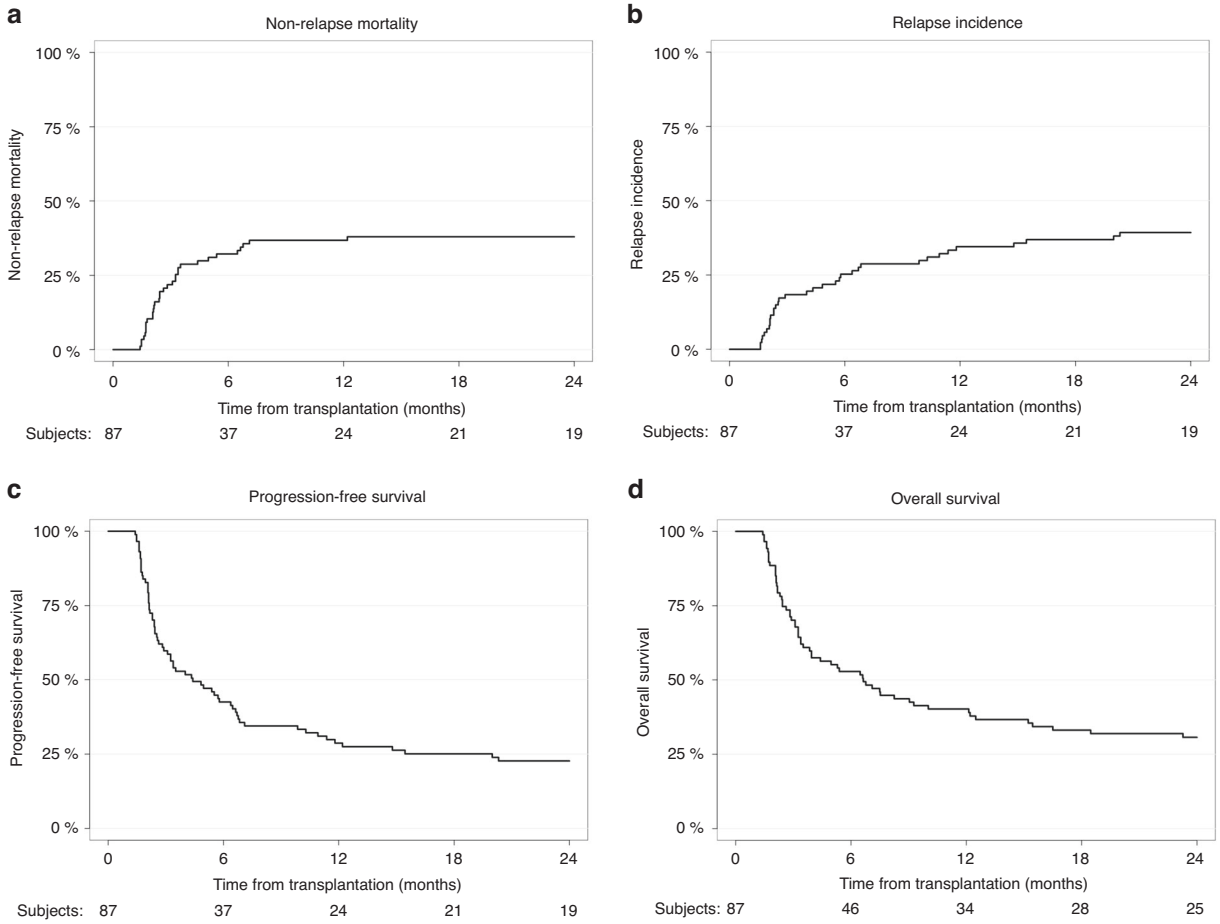

Fig. 1 Outcomes of patients with graft failure after CBT. Outcomes are given from the day of the first transplantation. However, given the selected definition of graft failure in the current study (i.e. absence of neutrophil engraftment at day 42 and no prior leukemia relapse), no events occurred during the first 42 days for overall survival, progression-free survival, relapse incidence or nonrelapse mortality. **a** Nonrelapse mortality. **b** Relapse incidence. **c** Progression-free survival. **d** Overall survival.

relapse. Thirty-five patients had AML and 11 had ALL. Median time (interquartile range (IQR)) from first CBT to second allogeneic HSCT was 60 (49–71) days. Four patients were given a myeloablative (without TBI)-based conditioning while 41 patients received a RIC regimen (1 missing). Stem cell source included single ($n = 10$) or double ($n = 11$) CBT, HLA-haploidentical donor ($n = 13$), unrelated donor ($n = 8$), HLA-identical sibling donor ($n = 2$), or mismatched related donor ($n = 2$). Incidence of neutrophil engraftment at days 30 and 100 after second transplantation was 64% (95% CI 47–76%) and 73% (95% CI 56–84%), respectively. NRM was 26% (95% CI 14–39%) at 3 months and 40% (95% CI 25–54%) at 1-year (Fig. 3). Regarding relapse incidence, the figures were 12% (95% CI 4–23%) and 24% (95% CI 12–37%), respectively. One-year and 2-year OS and PFS from second transplantation were 41% (95% CI 29–58%) and 34% (95% CI 22–51%) for OS and 36% (95% CI 25–54%) and 34% (95% CI 22–52%) for PFS, respectively, in patients given a salvage second transplantation ($n = 46$).

Given the small number of patients in each group, it remains hazardous to formally compare outcomes according to donor type for the second transplantation. Three-month and 1-year OS was 77% (95% CI 57–100%) and 46% (95% CI 26–83%) in HLA-haploidentical recipients ($n = 13$), 60% (95% CI 36–100%) and 40% (95% CI 19–85%) in single CBT recipients ($n = 10$), and 36% (95% CI 17–79%) and 27% (95% CI 10–72%) in double CBT recipients ($P = 0.39$) ($n = 11$).

DISCUSSION

Although it has been well established that graft failure is not infrequent in adult patients offered CBT in comparison to other transplantation approaches [6], few studies to date have investigated the outcome of patients experiencing graft failure after CBT. It was the aim of the current study. Based on a prior study from our group that demonstrated that subsequent neutrophil engraftment was infrequent in CBT patients without neutrophil recovery at day 42 after CBT [7], we defined graft failure for the current study as absence of neutrophil recovery without leukemia recurrence at day 42 after transplantation.

Our study showed that approximately one third of CBT patients with graft failure survived without leukemia recurrence beyond 2 years after transplantation. These results are in line with a prior analysis from the Massachusetts General Hospital, reporting a 3-year PFS of 23% and a 3-year OS of 37% in patients experiencing graft failure after CBT [13].

A salvage second transplantation could be performed in 45% of the patients in the first 3 months following the first transplantation while 2-year PFS after salvage transplantation was 34%. Unfortunately, the small number of patients who received salvage second transplantation precluded us formally comparing the impact of donor type on second transplantation outcomes. It should be noted that a recent study from Eurocord reported a 3-year OS at 29% in patients receiving CBT as treatment for graft

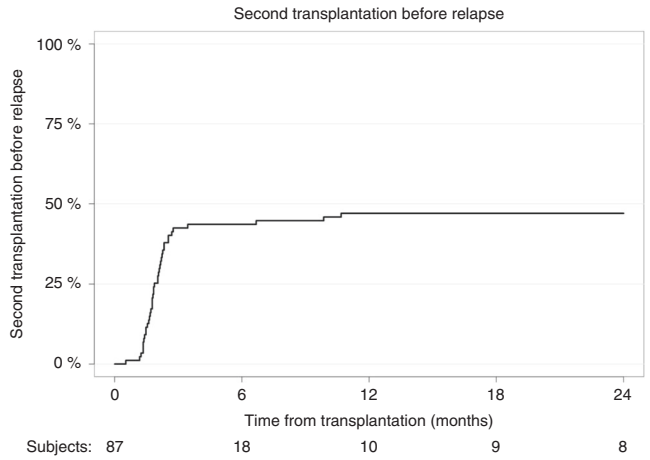

Fig. 2 Incidence of second transplantation. Cumulative incidence of second transplantation before relapse in patients with graft failure after CBT.

failure after a first allogeneic transplantation given as treatment for an hematological malignancy ($n = 141$) [14]. In addition, another study reported 1-year OS of 47% in patients given salvage haploidentical transplantation with post-transplant cyclophosphamide as treatment for graft failure after a first allogeneic transplantation [15]. These observations are consistent to what was observed in the current study.

Several factors were identified as predicting better PFS and/or OS after graft failure. Firstly, not surprisingly, being in CR at CBT was associated with better OS due to lower risk of relapse. This is in line with previous observations showing poor outcomes in CBT patients with active leukemia at transplantation [10]. Secondly, use of a RIC regimen before first CBT was associated with lower NRM and better OS. Prior studies have assessed the impact of conditioning intensity in patients offered CBT for AL. These studies showed similar LFS and OS with myeloablative versus RIC [16, 17].

This study has several limitations. The first is that we missed chimerism data for a high proportion of patients as well as data on cell dose infused and HLA-compatibility. It should be noted that one-quarter of the patients received a total nucleated cell (TNC) dose ≤2.5 × 10^7/kg. Another limitation was that we did not have data on donor-specific antibodies. In addition, the number of patients who received a second transplantation for graft failure was relatively small precluding a formal comparison of the impact of stem cell source for the second transplantation.

The field of CBT is evolving, and several areas of progress are likely to decrease the rate of graft failure after CBT. Optimization of the conditioning regimen has been associated with a much lower incidence of graft failure (<5%) [18]. Furthermore, impressive progress has been made in the field of CBT expansion [19–22], with recent studies suggesting consistent engraftment (i.e. no graft failure) following transplantation of a single expanded CBT units expanded ex vivo with SR-1 (an hematopoietic stem cell self-renewal agonist) [21], UM171 (another hematopoietic stem cell self-renewal agonist) [22, 23] or nictotinamide [24, 25].

In summary, in this retrospective study we observed that one-quarter of patients with graft failure after CBT for AL remained alive without relapse 2 years later. Recent progress in the field of CBT expansion is promising and might solve the problem of slow engraftment/graft failure associated with CBT and renew the interest of CBT for patients with acute leukemia.

Table 2. Multivariate Cox models for outcomes in the 87 patients with graft failure after first CBT.

Variables	Modalities	PFS		OS		Relapse incidence		NRM	
		HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Type of leukemia	ALL vs AML	0.82 [0.42–1.61]	0.57	0.95 [0.47–1.9]	0.88	0.71 [0.26–1.92]	0.5	0.92 [0.37–2.33]	0.86
CR at transplantation	Yes vs No	0.58 [0.32–1.05]	0.073	0.45 [0.25–0.83]	0.01	0.44 [0.19–1.01]	0.053	0.79 [0.33–1.89]	0.59
Patient age	5 yrs increment	1.08 [0.96–1.21]	0.22	1.09 [0.96–1.23]	0.17	1.02 [0.87–1.18]	0.83	1.16 [0.97–1.39]	0.1
Patient sex	Female versus male	0.7 [0.41–1.18]	0.18	0.67 [0.39–1.15]	0.15	0.72 [0.35–1.48]	0.37	0.69 [0.32–1.47]	0.33
Intensity of the conditioning	RIC vs MAC	0.63 [0.36–1.1]	0.1	0.51 [0.29–0.91]	0.023	1.25 [0.59–2.67]	0.56	0.26 [0.1–0.65]	0.004

MAC myeloablative conditioning, *RIC* reduced-intensity conditioning, *OS* overall survival, *PFS* progression-free survival, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *Yrs* years, *CR* complete remission, *NRM* nonrelapse mortality, *RIC* reduced-intensity conditioning, *MAC* myeloablative conditioning.
Outcomes are calculated from day 42 after first CBT.

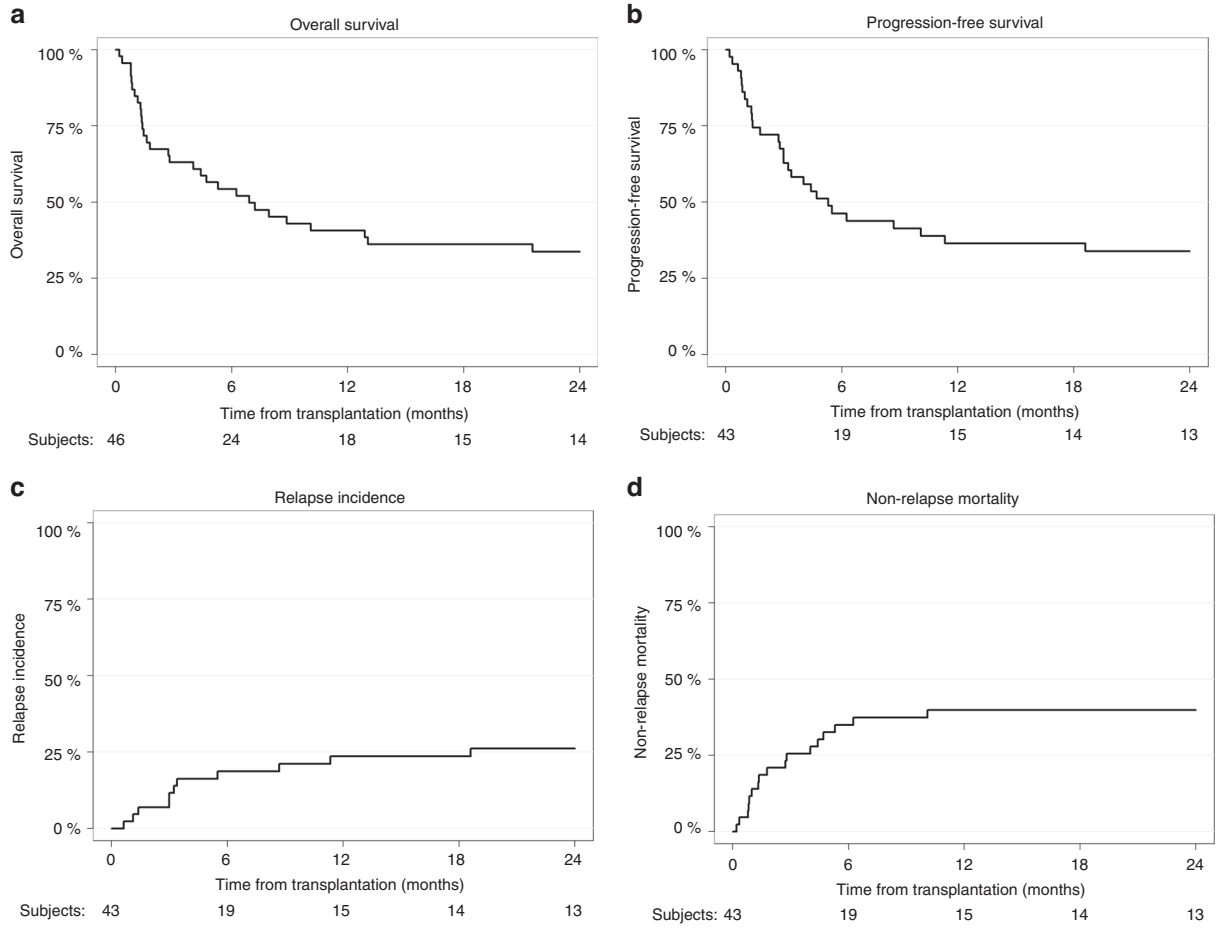

Fig. 3 Outcomes of patients with salvage second transplantation as treatment for graft failure after CBT. Day 0 is the day of the second transplantation. **a** Overall Survival. **b** Progression-free survival. **c** Relapse incidence. **d** Nonrelapse mortality.

DATA AVAILABILITY

CP, ML, MMo and AN had full access to all the data in the study (available upon data specific request).

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AUTHOR CONTRIBUTIONS

FB wrote the manuscript, designed the study, and interpreted the data. CP and ML designed the study, performed the statistical analyses, interpreted the data, and edited the manuscript. AR, EG, MMo and AN designed the study, interpreted the data, and edited the manuscript. JS, RS, CP, MMi, JHB, CF and WA reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

COMPETING INTERESTS

FB has received travel grants and/or speaker honoraria from Celgene, Abbvie, Novartis, Pfizer and Sanofi. The other authors declare that they have no relevant conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The scientific boards of the ALWP of the EBMT approved this study. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41409-023-02000-9.

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