# Cord blood transplantation for AML: comparable LFS in patients with de novo versus secondary AML in CR1, an ALWP/EBMT study

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ORIGINAL PAPER

# Cord blood transplantation for AML: Comparable LFS in patients with de novo versus secondary AML in CR1, an ALWP/EBMT study

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**Summary**
We investigated whether secondary versus de novo acute myeloid leukaemia (AML) would be associated with poor outcomes in adult acute AML patients in first complete remission (CR1) receiving unrelated cord blood transplantation (CBT). This is a retrospective study from the acute leukaemia working party of the European Society

Frédéric Baron and Arnon Nagler contributed equally to the work.

for Blood and Marrow Transplantation. Inclusion criteria included adult at first allogeneic haematopoietic cell transplantation between 2000 and 2021, unrelated single or double unit CBT, AML in CR1, no ex vivo T-cell depletion and no post-transplant cyclophosphamide. The primary end-point of the study was leukaemia-free survival (LFS). A total of 879 patients with de novo ($n = 696$) or secondary ($n = 183$) AML met the inclusion criteria. In multivariable analyses, sAML patients had non-significantly different LFS (HR = 0.98, $p = 0.86$), overall survival (HR = 1.07, $p = 0.58$), relapse incidence (HR = 0.74, $p = 0.09$) and non-relapse mortality (HR = 1.26, $p = 0.13$) than those with de novo AML. Our results demonstrate non-significantly different LFS following CBT in adult patients with secondary versus de novo AML.

**KEYWORDS**
acute myeloid leukaemia, AML, cord blood transplantation, de novo, secondary

## INTRODUCTION

Secondary acute myeloid leukaemia (sAML) includes AML occurring after prior myelodysplastic syndrome or myeloproliferative neoplasm as well as AML occurring after exposure to radiation or chemotherapy.[1] Its incidence is increasing given the improvement in cancer survival rates.[2] Secondary AML has been associated with poorer outcomes than de novo AML.[1] Potential reasons include a high frequency of clonal haematopoiesis, which can prolong the duration of myelosuppression after intensive chemotherapy; a higher prevalence of comorbidities; the possibility of primary disease recurrence in case of sAML occurring after a prior malignancy; and a higher prevalence of poor-risk cytogenetics and TP53 mutations.[1,3,4]

Although allogeneic haematopoietic cell transplantation (allo-HCT) has remained the treatment of choice for fit patients with sAML in first complete remission (CR1) for intermediate and unfavourable-risk disease,[1] prior studies have demonstrated inferior leukaemia-free survival (LFS) following allo-HCT for secondary versus de novo AML among patients given grafts from either a human leukocyte antigen (HLA)-identical sibling or unrelated donor.[5]

It is now well established that the cure offered to AML patients by an allo-HCT relies mainly on graft-versus-leukaemia (GvL) effects.[6] This is particularly the case in patients with sAML.[7] Prior studies have associated unrelated cord blood transplantation (CBT) with high GvL effects[8] and with encouraging transplantation outcomes in sAML.[9] These observations prompted us to investigate whether secondary versus de novo AML would also be a risk factor for poor outcomes in adult AML patients in CR1 receiving unrelated CBT.

## METHODS

### Inclusion criteria

This is a retrospective study from the acute leukaemia working party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT registry is a voluntary working society of more than 600 transplant centres, participants of which are required once a year to report all consecutive HCTs and follow-up. The EBMT Med A/B standardized data collection forms are submitted to the registry by transplant centre personnel following written informed consent from patients in accordance with centre ethical research guidelines. The accuracy of the data is assured by the individual transplant centres and by quality control measures such as regular internal and external audits. Audits are routinely performed to check for data accuracy.

Inclusion criteria were adult patients (defined as ≥18 years of age at first transplantation), first allo-HCT with single or double unrelated CBT between 2000 and 2021, de novo or sAML in CR1, no ex vivo T-cell depletion and no post-transplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis (since this was introduced only recently in the CBT setting).

### Ethics approval and consent to participate

The scientific board of the ALWP of the EBMT approved this study. All patients gave informed consent to participate in retrospective studies.

### Definitions

Myeloablative conditioning (MAC) was defined as regimens combining with either ≥8 Gy total body irradiation (TBI), ≥9.6 mg/kg busulfan or as defined by the centres for other conditioning regimens. Acute and chronic GVHD were graded by the transplant centres according to previously reported criteria.[10]

### Statistical analyses

Analyses included data from all patients meeting the inclusion/exclusion criteria. Quantitative variables were described

as median and quartiles 1 and 3, and qualitative variables as number and frequency. Patient, disease and transplant-related characteristics for the cohorts (de novo vs. sAML) were compared using the chi-squared test for categorical variables and the Wilcoxon–Mann–Whitney test for quantitative variables. A comparison of the cytogenetic risk between the two groups was done with a Cochran–Armitage trend test.

The primary end-point was LFS. Secondary end-points included GVHD, relapse incidence (RI), non-relapse mortality (NRM), overall survival (OS) and GVHD-free relapse-free survival (GRFS). LFS was defined as survival with no evidence of relapse or progression. Relapse was defined as the presence of 5% bone marrow blasts and/or the reappearance of the underlying disease. NRM was defined as death without evidence of relapse or progression. OS was defined as the time from transplantation to death, regardless of the cause. Events in the composite end-point GRFS included grade III–IV acute GVHD, severe chronic GVHD, relapse and death, whichever occurred first, as previously reported.[11] The cytogenetic risk group was defined using the Medical Research Council (MRC) classification modified according to Canaani et al.[12]

Patients were censored at the time of last follow-up. The Kaplan–Meier method was used to estimate the probabilities of LFS, OS and GRFS. Cumulative incidence functions were used to estimate the end-points of RI, NRM, acute and chronic GVHD, to accommodate for competing risks. RI and NRM were mutually competing events. To study acute and chronic GVHD, we considered relapse and death as competing events. The median follow-up was estimated using the reverse Kaplan–Meier method.

A Cox proportional hazards model was used for multivariable regression. Variables included were AML type (dnAML vs. sAML), cytogenetic group, number of CB unit, use of ATG, TBI, regimen intensity, age at HCT, time from diagnosis to HCT and year of HCT. A frailty term has been included in order to take into account the centre effect. A missing category was created for the missing or failed cytogenetic test. We elected not to include the HCT-CI score in the models since the data were missing for 49% of the patients and since prior solid tumour (which is by definition linked to sAML) is an important component of the HCT-CI score (providing 3 points).[13] All tests were two sided. The type I error rate was fixed at 0.05 for the determination of factors significantly associated with time to event outcomes. Results were presented as the Hazard Ratio (HR) and their 95% confidence intervals. Statistical analyses were performed with R 4.0.2 (R Development Core Team) software.

# RESULTS

## Patients

A total of 879 patients with de novo ($n=696$) or secondary ($n=183$) AML met the inclusion criteria (Table 1). In comparison with de novo AML patients, those with sAML were older (54.7 vs. 47.2 years old, $p<0.001$), were transplanted sooner after diagnosis (median of 5 months vs. 5.6 months, $p=0.003$), received more frequently double CBT (62 vs. 47%, $p<0.001$) and were transplanted more frequently following RIC (63% vs. 50%, $p=0.002$). Importantly, the proportion of patients with poor-risk cytogenetic[12] was not different in the two groups (39 vs. 35%).

## Engraftment and GVHD

The 30- and 60-day cumulative engraftment in de novo versus sAML were 69% and 90% versus 68% and 90% respectively.

The 180-day cumulative incidences of grade II–IV and grade III–IV acute GVHD were 37% and 14% in patients with de novo AML versus 36% and 16% in those with sAML. In multivariable analysis, the use of anti-thymocyte globulin (ATG) was associated with lower incidence of grades II–IV (HR = 0.56, 95% CI 0.38–0.82, $p=0.003$) and III–IV (HR = 0.43, 95% CI 0.23–0.81, $p=0.01$) acute GVHD (Table 2).

The 2-year cumulative incidences of chronic and extensive chronic GVHD were 28% and 12% in patients with de novo AML versus 26% and 14% in those with sAML. In multivariable analysis, the use of a myeloablative conditioning was associated with a higher incidence of extensive chronic GVHD (HR = 1.92, 95% CI 1.09–3.38, $p=0.02$) (Table 2).

## Relapse incidence and NRM

The 2-year cumulative incidence of relapse was 26% in patients with de novo AML versus 23% in those with sAML (Figure 1). In multivariable analysis, in comparison with de novo AML patients, those with sAML had a non-significantly different RI (HR = 0.74, 95% CI 0.52–1.05, $p=0.09$) (Table 3). However, poor-risk cytogenetic was associated with a higher RI (HR = 2.03, 95% CI 1.48–2.79, $p<0.001$). In contrast, the use of a myeloablative conditioning regimen was associated with a lower RI (HR = 0.59, 95% CI 0.41–0.84, $p=0.004$).

The 2-year cumulative incidence of NRM was 26% in patients with de novo AML versus 33% in those with sAML (Figure 1). In multivariable analysis, in comparison with de novo AML patients, those with sAML had a non-significantly different NRM (HR = 1.26, 95% CI 0.94–1.70, $p=0.13$) (Table 3). In contrast, the use of ATG (HR = 1.69, 95% CI 1.13–2.51, $p=0.01$), older age at transplantation (HR per 10-year increment = 1.16, 95% CI 1.04–1.29, $p=0.008$) and longer time from diagnosis to transplantation (HR per 2-month increment = 1.12, 95% CI 1.04–1.21, $p=0.004$) were each associated with higher NRM.

## LFS, OS and GRFS

The 2-year LFS was 48% in patients with de novo AML versus 44% in those with sAML (Figure 1). In

**TABLE 1** Patient, disease and transplant characteristics.

| Variables | Modalities | *N* = 879 | de novo (*N* = 696) | sAML (*N* = 183) | Test |
|---|---|---|---|---|---|
| Age at HSCT | Median [IQR] | 48.5 [36.1–58.8] | 47.2 [34.3–57.8] | 54.7 [43.4–60.7] | <0.001 |
| | (range) | (18.1–74) | (18.1–74) | (18.6–73.2) | |
| Patient sex | Female | 457 (52) | 359 (51.6) | 98 (53.6) | 0.63 |
| | Male | 422 (48) | 337 (48.4) | 85 (46.4) | |
| Year of HCT | Median [IQR] | 2012 [2009–2015] | 2012 [2009–2015] | 2012 [2009–2015.5] | 0.93 |
| | (range) | (2000–2021) | (2000–2021) | (2000–2021) | |
| Cytogenetic AML classification | Good | 36 (6) | 30 (6.1) | 6 (5.4) | 0.36 |
| | Intermediate | 355 (58.7) | 293 (59.4) | 62 (55.4) | |
| | Poor | 214 (35.4) | 170 (34.5) | 44 (39.3) | |
| | Missing | 274 | 203 | 71 | |
| CMV patient | Negative | 287 (35) | 227 (35.2) | 60 (34.3) | 0.82 |
| | Positive | 533 (65) | 418 (64.8) | 115 (65.7) | |
| | Missing | 59 | 51 | 8 | |
| Karnofsky performance score | <90 | 160 (22.3) | 119 (20.8) | 41 (28.3) | 0.055 |
| | ≥90 | 556 (77.7) | 452 (79.2) | 104 (71.7) | |
| | Missing | 163 | 125 | 38 | |
| Months between diag and HCT | Median [IQR] | 5.5 [4.2–7] | 5.6 [4.4–7] | 5 [3.8–6.9] | 0.003 |
| | (range) | (1.6–23.9) | (2–23.9) | (1.6–20.2) | |
| Myeloablative regimen | No | 466 (53.1) | 350 (50.4) | 116 (63.4) | 0.002 |
| | Yes | 411 (46.9) | 344 (49.6) | 67 (36.6) | |
| | Missing | 2 | 2 | 0 | |
| TBI | No | 357 (40.7) | 292 (42) | 65 (35.5) | 0.11 |
| | Yes | 521 (59.3) | 403 (58) | 118 (64.5) | |
| | Missing | 1 | 1 | 0 | |
| In vivo TCD | No | 524 (62.6) | 411 (62.2) | 113 (64.2) | 0.62 |
| | ATG | 313 (37.4) | 250 (37.8) | 63 (35.8) | |
| | Missing | 42 | 35 | 7 | |
| Number of CB | CB | 435 (49.5) | 366 (52.6) | 69 (37.7) | <0.001 |
| | Double CB | 444 (50.5) | 330 (47.4) | 114 (62.3) | |
| HLA CB (sero A and B, allelic DRB1) | CB 6/6 | 27 (4) | 24 (4.5) | 3 (2.1) | Not done |
| | CB 5/6 | 105 (15.6) | 90 (16.9) | 15 (10.7) | |
| | CB ≤ 4/6 | 187 (27.7) | 158 (29.6) | 29 (20.7) | |
| | Double CB (6/6; 6/6) | 7 (1) | 3 (0.6) | 4 (2.9) | |
| | Double CB (6/6; 5/6) | 18 (2.7) | 15 (2.8) | 3 (2.1) | |
| | Double CB (6/6; ≤4/6) | 2 (0.3) | 2 (0.4) | 0 (0) | |
| | Double CB (6/6; NA) | 6 (0.9) | 3 (0.6) | 3 (2.1) | |
| | Double CB (5/6; 5/6) | 62 (9.2) | 42 (7.9) | 20 (14.3) | |
| | Double CB (5/6; ≤4/6) | 69 (10.2) | 48 (9) | 21 (15) | |
| | Double CB (5/6; NA) | 27 (4) | 19 (3.6) | 8 (5.7) | |
| | Double CB (≤4/6; ≤4/6) | 122 (18.1) | 101 (18.9) | 21 (15) | |
| | Double CB (≤4/6; NA) | 42 (6.2) | 29 (5.4) | 13 (9.3) | |
| | Missing | 205 | 162 | 43 | |
| GVHD prophylaxis | CSA + MMF | 583 (69.7) | 448 (67.8) | 135 (76.7) | ND |
| | CSA | 179 (21.4) | 153 (23.1) | 26 (14.8) | |
| | CSA + MTX | 22 (2.6) | 19 (2.9) | 3 (1.7) | |
| | CSA + MTX + MMF | 9 (1.1) | 5 (0.8) | 4 (2.3) | |
| | MMF + SIRO | 11 (1.3) | 9 (1.4) | 2 (1.1) | |
| | MMF + TACRO | 9 (1.1) | 9 (1.4) | 0 (0) | |
| | Other | 24 (2.9) | 18 (2.7) | 6 (3.4) | |
| | Missing | 42 | 35 | 7 | |

Abbreviations: AML, acute myeloid leukaemia; CB, cord blood; CMV, cytomegalovirus; HCT, haematopoietic cell transplantation; HSCT, hematopoietic stem cell transplantation; in vivo TCD, in vivo T-cell depletion (i.e. anti-thymocyte globulin); Months between diag, months between diagnosis and HCT; NA, not available; sAML, secondary AML; TBI, total body irradiation.

(Continues)

**TABLE 2** Multivariable analyses for GVHD.

| Variables | Modalities | AGVH II–IV | | AGVH III–IV | | CGVH | | Ext CGVH | |
|---|---|---|---|---|---|---|---|---|---|
| | | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* |
| AML type | de novo | 1 | | 1 | | 1 | | 1 | |
| | sAML | 0.92 (0.68–1.23) | 0.57 | 1.12 (0.70–1.77) | 0.64 | 0.83 (0.58–1.17) | 0.28 | 1.31 (0.82–2.10) | 0.25 |
| Cytogenetic AML | Good/int | 1 | | 1 | | 1 | | 1 | |
| | Poor | 0.87 (0.65–1.16) | 0.34 | 0.94 (0.59–1.51) | 0.81 | 0.97 (0.67–1.40) | 0.86 | 0.96 (0.57–1.64) | 0.89 |
| | NA/failed | 1.02 (0.76–1.37) | 0.9 | 1.16 (0.72–1.85) | 0.55 | 1.45 (1.04–2.01) | **0.03** | 1.15 (0.72–1.82) | 0.56 |
| Number of CB | CB | 1 | | 1 | | 1 | | 1 | |
| | Double CB | 1.03 (0.76–1.41) | 0.83 | 0.74 (0.46–1.20) | 0.23 | 1.07 (0.73–1.57) | 0.71 | 0.98 (0.57–1.69) | 0.95 |
| In vivo TCD | No | 1 | | 1 | | 1 | | 1 | |
| | Yes | 0.56 (0.38–0.82) | **0.003** | 0.43 (0.23–0.81) | **0.009** | 1.38 (0.89–2.14) | 0.16 | 1.66 (0.89–3.09) | 0.11 |
| TBI | No | 1 | | 1 | | 1 | | 1 | |
| | Yes | 1.35 (0.89–2.04) | 0.16 | 1.33 (0.69–2.54) | 0.39 | 1.52 (0.94–2.46) | 0.09 | 1.32 (0.68–2.59) | 0.41 |
| Myeloablative regimen | No | 1 | | 1 | | 1 | | 1 | |
| | Yes | 1.21 (0.87–1.68) | 0.26 | 1.01 (0.61–1.67) | 0.98 | 1.43 (0.96–2.12) | 0.08 | 1.92 (1.09–3.38) | **0.02** |
| Age at HCT (effect for 10 year increment) | | 1.04 (0.94–1.14) | 0.46 | 0.90 (0.78–1.05) | 0.18 | 1.09 (0.97–1.23) | 0.14 | 1.14 (0.96–1.36) | 0.12 |
| Diag to HCT (effect for 2 month increment) | | 0.97 (0.89–1.06) | 0.52 | 1.02 (0.89–1.17) | 0.75 | 1.00 (0.90–1.11) | 0.99 | 1.02 (0.88–1.20) | 0.76 |
| Year (effect for 5 year increment) | | 1.11 (0.95–1.30) | 0.18 | 1.22 (0.95–1.56) | 0.11 | 1.02 (0.84–1.25) | 0.82 | 0.97 (0.74–1.29) | 0.86 |

Abbreviations: AGVH, acute graft-versus-host disease; AML, acute myeloid leukaemia; CB, cord blood; cGVH, chronic graft-versus-host disease; HCT, haematopoietic cell transplantation; in vivo TCD, in vivo T-cell depletion (i.e. anti-thymocyte globulin); int, intermediate; NA, not applicable; TBI, total body irradiation.

*Note*: Bold values indicate significance of $p < 0.05$.

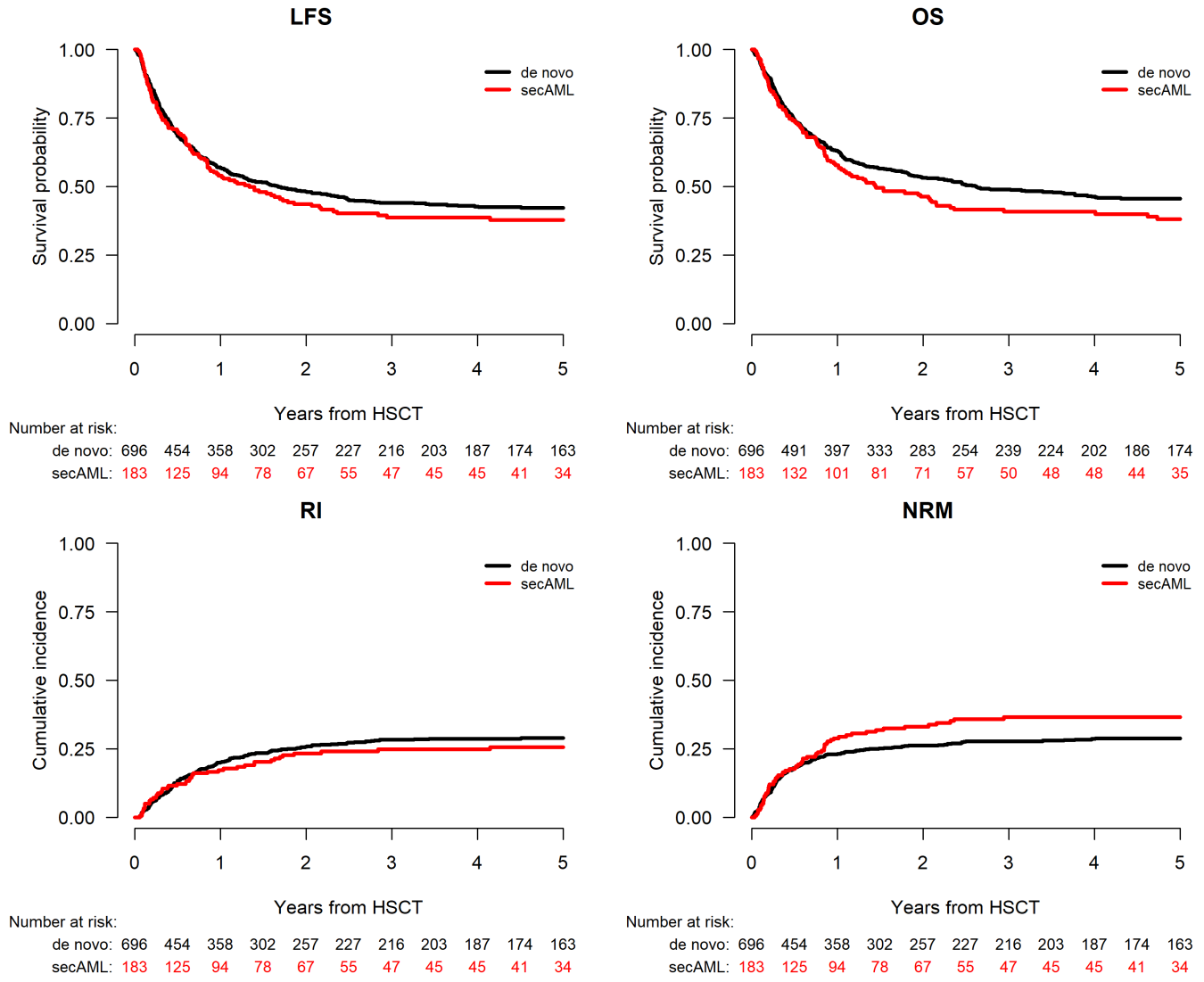


**FIGURE 1** Comparison of relapse incidence (RI), non-relapse mortality (NRM), leukaemia-free survival (LFS) and overall survival (OS) in patients receiving CBT for de novo versus secondary acute myeloid leukaemia. HSCT, hematopoietic stem cell transplantation. [Colour figure can be viewed at wileyonlinelibrary.com]

multivariable analysis, in comparison with de novo AML patients, those with sAML had a non-significantly different LFS (HR = 0.98, 95% CI 0.78–1.23, $p = 0.86$) (Table 3). In contrast, poor-risk cytogenetic (HR = 1.43, 95% CI 1.14–1.79, $p = 0.002$), the use of ATG (HR = 1.50, 95% CI 1.12–2.01, $p = 0.007$) and older age at transplantation (HR = 1.11, 95% CI 1.03–1.20, $p = 0.008$) were each associated with lower LFS.

At 2-year, OS was 53% in patients with de novo AML versus 46% in those with sAML. In multivariable analysis, in comparison with de novo AML patients, those with sAML had a non-significantly different OS (HR = 1.07, 95% CI 0.85–1.34, $p = 0.58$). In contrast, poor-risk cytogenetic (HR = 1.34, 95% CI 1.06–1.69, $p = 0.01$), the use of ATG (HR = 1.48, 95% CI 1.09–2.01, $p = 0.01$) and older age at transplantation (HR = 1.14, 95% CI 1.05–1.24, $p < 0.001$) each associated with lower OS. Main causes of death were close in the two groups of patients and included original disease (46%), infection (25%) and GVHD (17%) (Table 4).

Finally, 2-year GRFS was 37% in patients with de novo AML versus 32% in those with sAML (HR = 1.09, 95% CI 0.88–1.34, $p = 0.44$ in multivariable analysis) (Table 3).

## DISCUSSION

Prior studies have demonstrated inferior LFS following allo-HCT for secondary versus de novo AML among patients given grafts from either HLA-identical sibling, unrelated donor or HLA-haploidentical donor.[5] Given that CBT has been associated with high GvL effects,[14,15] we investigated whether sAML was also a high-risk factor in the CBT setting. Several observations were made.

First, we observed non-significantly different LFS in patients with de novo or sAML. The 2-year LFS of 48% in de novo AML patients in CR1 in the current study seems low. Indeed, a recent study comparing transplantation outcomes in de novo versus sAML patients receiving grafts

**TABLE 3** Multivariable analyses for transplantation outcomes.

| | | LFS | | OS | | RI | | NRM | | GRFS | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variables** | **Modalities** | **HR (95% CI)** | ***p*** | **HR (95% CI)** | ***p*** | **HR (95% CI)** | ***p*** | **HR (95% CI)** | ***p*** | **HR (95% CI)** | ***p*** |
| AML type | de novo | 1 | | 1 | | 1 | | 1 | | 1 | |
| | sAML | 0.98 (0.78–1.23) | 0.86 | 1.07 (0.85–1.34) | 0.58 | 0.74 (0.52–1.05) | 0.09 | 1.26 (0.94–1.70) | 0.13 | 1.09 (0.88–1.34) | 0.44 |
| Cytogenetic AML | Good/Int | 1 | | 1 | | 1 | | 1 | | 1 | |
| | Poor | 1.43 (1.14–1.79) | **0.002** | 1.34 (1.06–1.69) | **0.01** | 2.03 (1.48–2.79) | **<0.001** | 0.97 (0.70–1.36) | 0.87 | 1.24 (1.01–1.53) | 0.05 |
| | NA/Failed | 1.16 (0.93–1.44) | 0.19 | 1.14 (0.91–1.42) | 0.27 | 1.23 (0.87–1.73) | 0.24 | 1.06 (0.79–1.42) | 0.71 | 1.13 (0.91–1.39) | 0.27 |
| Number of CB | Single CB | 1 | | 1 | | 1 | | 1 | | 1 | |
| | Double CB | 0.94 (0.75–1.19) | 0.61 | 0.94 (0.74–1.19) | 0.61 | 0.94 (0.67–1.32) | 0.73 | 0.95 (0.68–1.31) | 0.75 | 0.87 (0.69–1.10) | 0.24 |
| In vivo TCD | No | 1 | | 1 | | 1 | | 1 | | 1 | |
| | Yes | 1.50 (1.12–2.01) | **0.007** | 1.48 (1.09–2.01) | **0.01** | 1.28 (0.81–2.02) | 0.29 | 1.69 (1.13–2.51) | **0.01** | 1.21 (0.92–1.59) | 0.18 |
| TBI | No | 1 | | 1 | | 1 | | 1 | | 1 | |
| | Yes | 1.07 (0.80–1.45) | 0.63 | 1.05 (0.77–1.43) | 0.76 | 1.24 (0.78–1.95) | 0.36 | 0.99 (0.66–1.49) | 0.96 | 1.23 (0.92–1.64) | 0.16 |
| Myeloablative regimen | No | 1 | | 1 | | 1 | | 1 | | 1 | |
| | Yes | 0.82 (0.64–1.05) | 0.12 | 0.89 (0.69–1.15) | 0.39 | 0.59 (0.41–0.84) | **0.004** | 1.11 (0.79–1.57) | 0.54 | 0.94 (0.74–1.18) | 0.58 |
| Age at HSCT (effect for 10-year increment) | | 1.11 (1.03–1.20) | **0.008** | 1.14 (1.05–1.24) | **<0.001** | 1.05 (0.95–1.18) | 0.34 | 1.16 (1.04–1.29) | **0.008** | 1.07 (1.01–1.15) | 0.06 |
| Diag to HSCT (effect for 2-month increment) | | 1.03 (0.96–1.09) | 0.41 | 1.04 (0.98–1.11) | 0.19 | 0.92 (0.83–1.03) | 0.15 | 1.12 (1.04–1.21) | **0.004** | 1.02 (0.96–1.09) | 0.51 |
| Year (effect for 5-year increment) | | 0.93 (0.83–1.05) | 0.24 | 0.91 (0.80–1.03) | 0.13 | 0.96 (0.81–1.15) | 0.67 | 0.91 (0.77–1.07) | 0.26 | 0.96 (0.85–1.07) | 0.45 |

Abbreviations: AML, acute myeloid leukaemia; CB, cord blood; GRFS, GVHD-free and relapse-free survival; HCT, haematopoietic cell transplantation; HSCT, hematopoietic stem cell transplantation; in vivo TCD, in vivo T-cell depletion (i.e. anti-thymocyte globulin); int, intermediate; LFS, leukaemia-free survival; NA, not applicable; NRM, non-relapse mortality; OS, overall survival; RI, relapse incidence; TBI, total body irradiation.

*Note*: Bold values indicate significance of $p < 0.05$.

**TABLE 4** Causes of death.

| Cause | Death ($N=445$) | de novo AML ($N=352$) | sAML ($N=93$) |
|---|---|---|---|
| Original disease | 200 (45.7) | 163 (47.1) | 37 (40.2) |
| Infection | 111 (25.3) | 85 (24.6) | 26 (28.3) |
| GVHD | 73 (16.7) | 54 (15.6) | 19 (20.7) |
| Secondary malignancy | 22 (5) | 19 (5.5) | 3 (3.3) |
| Haemorrhage | 9 (2.1) | 8 (2.3) | 1 (1.1) |
| Other HCT related | 23 (5.3) | 17 (4.9) | 6 (6.5) |
| Missing | 7 | 6 | 1 |

Abbreviations: AML, acute myeloid leukaemia; GVHD, graft-versus-host disease; HCT, haematopoietic cell transplantation; sAML, secondary AML.

from either HLA-identical sibling, HLA-matched unrelated donor, 1-HLA mismatched unrelated donor or T-cell repleted grafts from an HLA-haploidentical donor showed 2-year LFS rates of 55.1% for patients with de novo AML in CR1 versus 41.6% for those with sAML in CR1.[5] Looking at LFS components, neither RI nor NRM significantly differ between the two groups, although there was perhaps a suggestion for higher NRM but strikingly a suggestion for lower RI in sAML patients in multivariable analysis. The latter observation contrasts with what has been observed with other stem cell source[5] and suggests that CBT-driven GvL effects could be particularly efficient in sAML. This observation is in concordance with those reported by Milano et al. who observed high GvL effects following CBT in AML patients with minimal residual disease at transplantation,[8] although a study from our group evidenced that MRD positivity remained a significant risk factor following CBT for acute leukaemia.[16] Further, it should be noted that a direct comparison of haploidentical transplantation and CBT for sAML showed non-significantly different RI (as well as non-significantly different NRM, OS and LFS) with the two transplant approaches.[17] Accordingly, a recent study by our group did observe that haploidentical transplantation was able to overcome the poor prognosis associated with sAML, mirroring current observations with CBT.[18]

The current study also confirms several observations made in prior studies, such as the negative impact of ATG administration on NRM, LFS and OS,[19] higher RI but similar PFS in patients conditioned with RIC versus MAC regimen,[20] and non-significantly different outcomes in patients receiving single or double unit CBT.[21]

The current study also demonstrates a relatively high NRM associated with CBT for AML in CR1 (27% at 2 year) in patients transplanted from 2000, in concordance with prior observations.[22-24] Better CB unit selection, avoiding ATG in the conditioning and optimizing the conditioning regimen might help reducing NRM following CBT.[25-28] Moreover, recent advances in ex vivo cord blood expansion are also likely to reduce NRM not only by prompting engraftment and immune reconstitution but also by allowing the selection of HLA-matched unit.[29-31] As an example, a recent retrospective study demonstrated lower NRM with UM171-expanded CBT in comparison to CBT or HLA-matched unrelated transplantation.[32]

There are limitations in the current study, including the lack of data on cell dose, HLA-matching, molecular risk and MRD positivity at transplantation for many patients, precluding the inclusion of these criteria in the multivariable models. Another limitation linked to the registry nature of this study is that we cannot exclude that the decision to use CBT differed between de novo and sAML.

In summary, we observed non-significantly different LFS in AML patients in CR1 with de novo versus sAML offered a CBT. Interestingly, RI was not different in the two groups, suggesting a possible high GvL effects of CBT for patients with sAML.

## AUTHOR CONTRIBUTIONS

Frédéric Baron wrote the manuscript, designed the study and interpreted the data. Arnon Nagler, Mohamad Mohty and Fabio Ciceri designed the study, interpreted the data and edited the manuscript. Jacques-Emmanuel Galimard designed the study, performed the statistical analyses, interpreted the data and edited the manuscript. Jaime Sanz, Jurjen Versluis, Edouard Forcade, Patrice Chevallier, Anne Sirvent, Chloe Anthias, Jürgen Kuball, Sabine Furst, Alessandro Rambaldi, Jorge Sierra, Peter A. von dem Borne, Maria Pilar Gallego Hernanz, Thomas Cluzeau, Stephen Robinson, Anna Maria Raiola, Hélène Labussière-Wallet, Jenny L. Byrne, Jean-Valère Malfuson and Annalisa Ruggeri reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

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.

## DATA AVAILABILITY STATEMENT

JEG and MM had full access to all the data in the study (available upon data specific request).

## ETHICS STATEMENT

The scientific boards of the ALWP of the EBMT approved this study.

## PATIENT CONSENT STATEMENT

All patients gave informed consent to participate in retrospective studies.

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