

Unrelated Cord Blood Transplantation in Children, Adolescents, and Young Adults with Acute Leukemia or Myelodysplastic Syndrome: A Retrospective Comparative Study from the French Society for Bone Marrow Transplantation and Cellular Therapy Between Real-World Data and Previously Reported Results of a Randomized Clinical Trial

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Highlights

- In our previous randomized clinical trial (RCT), we concluded that single-unrelated cord blood transplantation (UCBT) with adequate cell dose is the standard of care for children and young adults with hematologic malignancies.
- The results in terms of graft failure, transplant-related mortality and overall survival reported in our RCT appear to be reproducible in real-world conditions.
- We confirm the superiority of TBI-Fludarabine-Cyclophosphamide as conditioning regimen in UCBT for pediatric acute lymphoblastic leukemia.

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Unrelated cord blood transplantation in children, adolescents, and young adults with acute leukemia or myelodysplastic syndrome: a retrospective comparative study from the French Society for Bone Marrow Transplantation and Cellular Therapy (SFGM-TC) between Real-World Data and previously reported results of a Randomized Clinical Trial

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Abstract

We previously reported results of a French randomized clinical trial (RCT) comparing the risk of transplantation failure (including transplant-related mortality (TRM), engraftment failure, and autologous recovery) in single and double unrelated cord blood (UCB) transplantation in children and young adults with hematologic malignancies. We concluded that single-UCB transplantation with an adequate cell dose is the standard of care, leading to a 70% two-year overall survival (OS). It remains unclear, however, whether RCT participants have better outcomes than comparable patients not treated in the setting of a clinical trial. We compared the characteristics and outcomes of RCT participants (n = 137) to a Francophone population-based registry of patients (real-world (RW) group) fulfilling the eligibility criteria used in our RCT and transplanted with one or two UCB units after a myeloablative conditioning (MAC) regimen between March 2015 (end of inclusion in the RCT) and February 2019 (n = 141). The primary endpoint was the two-year cumulative incidence (CI) of transplantation strategy failure as defined in our RCT. The two groups were comparable in terms of age, disease distribution, hematologic status at transplantation, follow-up, and HLA compatibility. Patients in the RW group were more likely to be transplanted with a single-unit UCB (87.9% versus 49.6%, $p < 0.001$) and to receive a radiation-free regimen (39.0% vs. 60.6%, $p < 0.001$). The two-year CI of transplantation strategy failure, TRM, and the two-year probability of OS were similar between the two groups, although the relapse risk was higher in the RW group (31.2% ± 7.7% vs. 20.4% ± 6.8%, $p = 0.01$), resulting in a significantly lower DFS (59.2% ± 8.4% vs. 69.3% ± 8.0%, $p = 0.047$). This difference remained statistically significant only in the group of patients with acute lymphoid leukemia (ALL) who did not receive the conditioning regimen recommended by the RCT (fludarabine 75 mg/m2, total body irradiation 12 Gy, cyclophosphamide 120 mg/kg). The results of our RCT appear to be reproducible in real-world conditions, provided that the same cord blood selection criteria and conditioning regimen are used.

Extended Abstract

1. Background: We previously reported results of a French randomized clinical trial (RCT) comparing the risk of transplantation failure (including transplant-related mortality (TRM), engraftment failure, and autologous recovery) in single and double unrelated cord blood (UCB) transplantation in children and young adults with hematologic malignancies. We concluded that single-UCB transplantation with an adequate cell dose is the standard of care, leading to a 70% two-year overall survival (OS). It remains unclear, however, whether RCT participants have better outcomes than comparable patients not treated in the setting of a clinical trial.

2. Objectives and Study design: We compared the characteristics and outcomes of RCT participants (n = 137) to a Francophone population-based registry of patients (real-world (RW) group) fulfilling the eligibility criteria used in our RCT and transplanted with one or two UCB units after a myeloablative conditioning (MAC) regimen between March 2015 (end of inclusion in the RCT) and February 2019 (n = 141). The primary endpoint was the two-year cumulative incidence (CI) of transplantation strategy failure as defined in our RCT.

3. Results: The two groups were comparable in terms of age, disease distribution, hematologic status at transplantation, follow-up, and HLA compatibility. Patients in the RW group were more likely to be transplanted with a single-unit UCB (87.9% versus 49.6%, $p < 0.001$) and to receive a radiation-free regimen (39.0% vs. 60.6%, $p < 0.001$). The two-year CI of

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transplantation strategy failure, TRM, and the two-year probability of OS were similar between the two groups, although the relapse risk was higher in the RW group (31.2% ± 7.7% vs. 20.4% ± 6.8%, p = 0.01), resulting in a significantly lower DFS (59.2% ± 8.4% vs. 69.3% ± 8.0%, p = 0.047). This difference remained statistically significant only in the group of patients with acute lymphoid leukemia (ALL) who did not receive the conditioning regimen recommended by the RCT (fludarabine 75 mg/m2, total body irradiation 12 Gy, cyclophosphamide 120 mg/kg).

4. Conclusion: The results of our RCT appear to be reproducible in real-world conditions, provided that the same cord blood selection criteria and conditioning regimen are used.

Introduction

Unrelated cord blood (UCB) has become an alternative source of stem cells for adults and children who require hematopoietic stem cell transplantation (HSCT) and who lack an HLA-matched donor[1]. Cord blood hematopoietic stem cells have several advantages over bone marrow or peripheral stem cells: 1/ immediate availability, 2/ lower degree of stringency in HLA matching requirements, 3/ less graft-versus-host disease, and 4/ enhanced graft-versus-leukemia effect[2]. The barrier of infused nucleated cell dose, a critical factor for engraftment and survival, can be overcome by transplantation of two UCB units in patients without a cord blood unit with a sufficient cell dose[3]. Several retrospective studies suggest that pediatric and adult patients with hematological malignancies have similar leukemia-free survivals after cord blood transplantation (CBT) or HLA-matched unrelated or haploidentical HSCT despite slower hematopoietic and immune reconstitution after CBT[4–7]. In a randomized study comparing transplantation with one versus two UCB units after myeloablative conditioning (MAC) in children and young adults less than 35 years of age with either acute leukemia in remission or myelodysplastic syndrome, our group reported 74.8% (two UCB) and 68.8% (one UCB) two-year overall survival[8]. The two-year transplantation strategy failure, defined as graft failure, > 80% blood recipient chimerism, or transplant-related mortality (TRM), was less than 20%.

Randomized clinical trials (RCT) are considered the gold standard for evaluation of the effectiveness of a new procedure because the investigators are able to reduce selection bias and confounding factors by utilizing strict patient inclusion criteria and methodologies[9]. As RCT do not accurately reflect real-world (RW) clinical practice, there is a need for observational studies to confirm that the results observed in randomized trials are reproducible[10]. To do so, we compared the clinical and outcome data of a Francophone population-based registry of patients fulfilling the eligibility criteria used in our RCT and transplanted with one or two UCB units after a MAC regimen, between March 2015 (end of inclusion in the randomized trial) and February 2019, to the previously reported data of the RCT.

Materials and Methods

Data source and patients

The current study focused on two populations of patients aged less than 35 years, with acute leukemia (AL) in complete remission or myelodysplastic syndrome (MDS) with < 20% bone marrow blasts, and transplanted with one or two unrelated cord blood units after a MAC regimen. Myeloablative conditioning was defined as a regimen comprising either fractionated total body irradiation (TBI) with a dose ≥ 8 Gy or a dose of i.v. busulfan > 6.4 mg/kg[11]. Donors and recipients were HLA matched for at least four out of six HLA-loci considering HLA-A and HLA-B at the antigen level and HLA-DRB1 at the allelic level.

The first group (RCT group) involved all patients included between February 2010 and February 2015 in our RCT comparing one versus two UCB units (n = 137) and the second group (RW group) involved patients treated between March 2015 and February 2019 (n = 141) and identified in the ProMISe database, including all centers affiliated with the French Society for Bone Marrow Transplantation and Cellular Therapy (SFGM-TC). All participating transplant centers received the synopsis of the study and provided their approval.

Outcomes

The primary endpoint of this study was the incidence of "transplantation strategy failure", defined as any of the four following events: transplant-related mortality (TRM), autologous recovery (defined as hematopoietic recovery with > 80% blood recipient chimerism), a second allogeneic transplantation, or infusion of an autologous stem cell rescue for engraftment failure. The secondary endpoints were relapse risk, TRM, overall survival (OS), disease-free survival (DFS), hematologic recovery and incidence of acute or chronic graft-versus-host disease (GvHD).

Relapse was defined as morphological or clinical evidence of disease after a period of complete remission (CR). TRM was defined as death from any cause in hematological remission.

OS was defined as the time from transplantation to the last follow-up or death. DFS was defined as the time from transplantation to relapse, death, or the date of the last follow-up.

Neutrophil recovery was defined as an absolute neutrophil count ≥ 0.5 G/L on three consecutive days. Platelet recovery was defined as a platelet count ≥ 20 G/L without transfusion support in the past seven days.

The diagnosis and grading of acute (aGvHD) and chronic GvHD (cGvHD) were assigned by the transplantation center using standard criteria[12].

Statistical Methods

The cumulative incidence (CI) function with competing events was used to estimate transplantation failure[13]. Comparisons were based on the Fine and Gray model[14]. The competing risk for transplantation failure was relapse. The same method was used to evaluate the relapse risk and TRM. The probabilities of OS and DFS were calculated using the Kaplan-Meier method and compared with the log-rank test[15]. All probabilities were at two years and provided with their 95% confidence interval (95% CI).

Results

Patient, Disease, and Transplantation Characteristics

Table 1 lists the patient, disease, and transplantation characteristics of the RCT (n = 137) and RW (n = 141) groups.

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The centers in the RW group were the same as those participating in the RCT. The baseline characteristics for patients treated in the trial versus non-trial were similar, such as age, sex, disease distribution, hematologic status at transplantation, degree of UCB/recipient HLA compatibility, and the time from diagnosis to UCB transplantation. As expected, in the RW population, there was a higher proportion of patients who were transplanted with a single UCB unit (87.9% vs. 49.6%, $p < 0.001$). The median number of infused total nucleated cells (TNC) per kilogram and the median number of infused $CD34^+$ cells per kilogram for the two groups are reported in Table 2. The median TNC cell dose was higher for the RW recipients of single-unit grafts compared with the trial participants (4.8×10^7 (range, 0.12 to 34.9) vs. 3.6×10^7 (range, 1.0 to 15.2), $p = 0.031$). Conversely, in the RCT cohort, recipients of double-unit grafts had a higher TNC and $CD34^+$ cell dose compared with the RW patients, due to study inclusion criteria (patients were eligible if they had at least 2 UCB that contained $> 3 \times 10^7$ TNC per kilogram for the first unit and $> 1.5 \times 10^7$ TNC per kilogram for the second). The mean follow-up duration from the HSCT was 752 days (range, 27 to 1,828) for the RW patients and 798 days (range, 15 to 1,830) for the RCT patients ($p = 0.46$).

Whereas all patients in the randomized trial received either TBI-Fludarabine-Cyclophosphamide (FluTBICy) (n = 83, 60.6%) or Busulfan-Cyclophosphamide-Anti-thymocyte globulin (BuCyATG) (n = 54, 39.4%) as conditioning regimen, we observed alternative regimens (in addition to these previous two) in sixty-one patients (43.3%) in the RW setting.

The FluTBICy regimen included fludarabine at 25 mg/m²/day from day -9 to day -7, TBI from day -6 to day -4, and cyclophosphamide at 60 mg/kg/day from day -3 to day -2. The TBI was fractionated over three days, with 2 Gy twice a day for a 12 Gy cumulative dose with lung shielding at 8 Gy. The BuCyATG regimen included busulfan from day -9 to day -6, with a dosage depending on the recipient's weight (< 9 kg: 1 mg/kg x 4/day; from 9 to 16 kg: 1.2 mg/kg x 4/day; from 16 to 23 kg: 1.1 mg/kg x 4/day), cyclophosphamide 50 mg/kg/day from day -5 to day -2, and rabbit anti-thymocyte globulin (ATG) 2.5 mg/kg/day from day -3 to day -1. GvHD prophylaxis consisted of cyclosporine A and steroid after BuCyATG as well as cyclosporine A and mycophenolate mofetil after FluTBICy.

Among the alternative regimens, 12 (8.5%) were treated with the association TBI-Etoposide (12 Gy TBI in six fractions over three days plus 60 mg/kg intravenous etoposide once a day) and 49 (34.8%) with a radiation-free regimen. The predominant chemoconditioning was Thiotepa-Busulfan-Fludarabine (intravenous fludarabine 30 mg/m² once a day for five days, thiotepa 5 mg/kg twice a day for one day, and busulfan for four days, with a dosage based on body weight), which was used especially for patients with ALL (n = 36/41, 87.8%). It should be noted that a lower proportion of patients in the RW cohort received a TBI-based conditioning regimen (39.0% vs. 60.6%, $p < 0.001$). Cyclosporine A plus mycophenolate mofetil was the most commonly used GvHD prophylaxis (n = 100, 71.4%) in the RW population. Overall, the use of ATG was comparable between both populations (39.4% vs. 38.3%, $p = 0.85$).

Primary endpoint analysis

The two-year CI of transplantation strategy failure was 14.9% ± 5.9% in the RW cohort and 10.9% ± 5.3% in the clinical trial cohort ($p = 0.35$) (Figure 1). The first classifying event was TRM, autologous recovery, or a second transplantation for engraftment failure in 11, 2, and 8 patients, respectively, of the RW cohort and 11, 2, and 2 patients, respectively, of the clinical trial cohort. In the RW group, among the 10 patients who experienced engraftment failure, four patients relapsed, leading to two deaths. Those requiring a second transplant for graft

failure had received a single cord blood unit. Five engraftment failures occurred in the 12 patients conditioned with the association TBI-Etoposide. In a subgroup analysis (RW cohort), diagnosis (AML/MDS vs. ALL), disease status at transplantation (CR1 vs. ≥ CR2), graft type (single UCB vs. double UCB transplantation), conditioning regimens (BuCyATG/FluCyTBI vs. alternative regimens), HLA compatibility (4/6 vs. 5/6 and 6/6), GvHD prophylaxis (with vs. without ATG), number of infused TNC and $CD34^+$ cells (below the median vs. above the median) had no discernible effect on primary endpoint (data not shown). Moreover, in the RW group, there was no significant difference between patients who experienced transplantation strategy failure and those who did not when comparing the median value of infused TNC and $CD34^+$ cells. Finally, we did not find a statistical difference in incidence of transplantation strategy failure according to the size of the center in terms of number of UCB transplants performed during the RW study period (results not shown).

Secondary endpoint analysis

The main post-transplantation outcomes are documented in Table 3.

The two-year probability of OS was similar between the RW and RCT groups (71.6% ± 7.6% vs. 72.9% ± 7.8%, p = 0.49), as was the two-year CI of TRM (7.8% ± 4.4% vs. 8.8% ± 4.8%, p = 0.74). The two-year CI of relapse was higher in the RW cohort (31.2% ± 7.7% vs. 20.4% ± 6.8%, p = 0.01), resulting in a significantly lower DFS (59.2% ± 8.4% vs. 69.3% ± 8.0%, p = 0.047). The median time from transplantation to relapse was 152 days (range, 25 to 1,188) for the RW patients and 156 days (range, 60 to 640) for the RCT patients (p = 0.4). A total of 78 patients died after transplantation: 43 in the RW population and 35 in the RCT cohort. Relapse was the most frequent cause of treatment failure in the two groups (Table 4).

The incidence of neutrophil recovery was 95.7% in the RW patients and 99.2% in the randomized study (p = 0.07). For platelet recovery, it was 88.5% and 94.5% (p = 0.08), respectively.

No statistically significant differences in acute GvHD were noted between the RW patients and the study participants (66.4% vs. 67.2%, p = 0.9). However, the incidence of chronic GvHD was significantly lower in the RW cohort (19.8% vs. 51.3%, p < 0.001).

Subgroup analysis

An exploratory subgroup analysis according to the type of leukemia was performed. In the ALL subgroup (n = 168), the only significant difference between the RW and the trial patients was the two-year CI of relapse, which was significantly higher for the RW patients compared to the trial participants (33.0% ± 9.9% vs. 18.8% ± 8.6%, p = 0.03) (Figure 2), but this higher incidence of relapse did not translate into a significantly decreased two-year DFS (72.2% ± 10.6% vs. 73.3% ± 9.6%, p = 0.262). In contrast, considering only ALL patients receiving FluTBICy as the conditioning regimen, there were no significant differences in relapse between the RCT and RW groups (15.4% ± 8.8% vs. 23.1% ± 13.4%, p = 0.27). We also compared outcomes after FluTBICy (n = 104) to those of other regimens (TBI-Etoposide or combined chemotherapy-only regimens) (n = 64). The relapse and mortality risk were significantly higher for the non-trial conditioning regimens (OR 0.49, 95% CI 0.28–0.86, p = 0.01).

In the AML-MDS subgroup (n = 110), we did not observe any significant differences, although there was a trend toward a lower DFS in the RW patients (68.7% ± 12.7% vs. 73.9% ± 11.8%, p = 0.077).

Discussion

We previously reported the results of a prospective randomized study designed to compare the outcomes of single versus double UCB transplantation in children and young adults less than 35 years of age with either acute leukemia in remission or MDS[8]. This trial failed to demonstrate a significant difference in the two-year cumulative incidence of transplantation strategy failure or the two-year post-transplantation survival between the two groups, and we concluded that single-UCB transplantation with an adequate cell dose is the standard of care, leading to a 70% two-year overall survival. These results confirmed those of another randomized study on the same topic conducted by Wagner et al. who found a similar one-year survival rate but a higher risk of GvHD after double-UCB transplantation compared to single-UCB transplantation[16]. Notably, the survival rates in both trials were higher than those reported in previous large, albeit mostly retrospective, studies[17,18]. Thus, some concerns can be raised regarding the reproducibility of RCT results in RW populations[19]. Differences in the outcomes of patients treated on versus off trials may be observed due to several potential biases: for example, inclusion of a highly selected patient population based on medical status, disease status, or compliance to treatment/medical follow-up, differences in care due to clinical trial participation, stringent rules for choosing the CB unit or homogeneous conditioning regimen. These potential limitations of RCT prompted us to compare the outcomes of patients treated in RW practice between March 2015 and February 2019 to those of the aforementioned randomized study. To our knowledge, there is a paucity of studies evaluating the reproducibility of the results of a RCT in children and young adults undergoing HSCT for hematologic malignancies.

We did not observe any difference between patients treated on-trial and off-trial in terms of the baseline characteristics such as age, sex, disease distribution, hematologic status at transplantation, the time from diagnosis to UCB transplantation, and the degree of UCB/recipient HLA compatibility. The administration, in the RW group, of several different conditioning regimens, instead of the two preparative regimens in the RCT group, represents a limitation of our study making the two groups not entirely comparable. As expected, there was a higher proportion of patients who were transplanted with a single-unit UCB (87.9% vs. 49.6%, $p < 0.001$) in the RW group, which included mostly pediatric patients. However, the median TNC/CD34+ cell dose was higher in this subgroup (RW recipients of single-unit grafts) than in the RCT cohort. The primary endpoint, namely, the cumulative incidence of transplantation strategy failure, including TRM and graft failure, was similar. This finding indicates that in most cases the UCB selection, in terms of cell dose and HLA compatibility, was done according to the recommendations of the RCT and that the good results reported in the RCT, in terms of engraftment and TRM, could be confirmed in the RW setting. It should be noted, however, that of the 12 patients who received the combination TBI-Etoposide, five experienced a graft failure or early graft loss and required a second transplantation. Etoposide is almost exclusively myelotoxic and was, therefore, introduced in the conditioning regimen to replace cyclophosphamide, which is a more immunosuppressive drug, with the objective of reducing the relapse risk after bone marrow transplantation for childhood ALL[20]. Several studies in the literature emphasize the crucial role of conditioning regimens and the need for intensive immune suppression before transplantation in order to achieve successful engraftment in UCB transplantation compared with other sources of stem cells[21–23]. ATG, often administered with the conditioning regimen in UCB transplantation, has been associated with a detrimental effect on survival, mainly as a result of an increase in infectious risk[24]. Kurtzberg et al. compared outcomes for recipients of a single UCB unit included in the BMT CTN 0501 trial (2006-2012) to those in a similar high-risk pediatric

malignancy population in an earlier multi-center trial of Cord Blood Transplantation (COBLT, conducted from 1994-2004). All patients received 1,350 cGy TBI and cyclophosphamide at 120 mg/kg, associated with equine ATG at 90 mg/kg in patients enrolled in COBLT and with fludarabine 75 mg/m² in those in BMT CTN 0501. They concluded that children receiving fludarabine had better engraftment and survival outcomes than those receiving ATG[18].

In our study, we observed a statistically comparable two-year OS for the two groups. The main difference between the outcome data of the two groups was a higher relapse risk in the RW cohort, which resulted in a significantly lower DFS. When performing a subgroup analysis according to the initial diagnosis, this difference remained statistically significant only in the group of patients with ALL. Considering patients with ALL on and off clinical trial, the only factor that had a significant impact on the relapse incidence was the conditioning regimen. Indeed, we observed a significantly higher relapse risk for patients who did not receive the conditioning regimen recommended by the trial, i.e., FluTBICy. Whereas the majority of ALL patients in the randomized trial received the combination FluTBICy as the conditioning regimen (n = 65/80, 81.3%), we observed several alternative conditioning regimens in the RW group because of competing protocols or center practices: 43% of ALL patients received a radiation-free regimen and 56% of ALL patients did not receive FluTBICy as the conditioning regimen. The benefit of TBI in reducing post-transplantation relapse in pediatric patients with high-risk ALL was recently demonstrated in a large international and multicenter randomized study (FORUM study) comparing TBI plus etoposide versus myeloablative chemotherapy (consisting of fludarabine, thiotepa, and either intravenous busulfan or treosulfan) before HSCT[25]. The lower risk of relapse and TRM in patients receiving TBI (the two-year cumulative incidence of TRM and relapse were 0.02 and 0.12, respectively, in patients receiving TBI and 0.09 and 0.33, respectively in patients receiving chemoconditioning, $p = 0.0269$ and $p < 0.001$) resulted in early termination of random assignment. Of note, only 4% of patients (n = 16) received cord blood as the stem cell source. Other retrospective studies have reported a positive role of TBI-containing versus non-TBI regimens, especially in UCB recipients. Eapen et al. compared the outcomes of children with acute leukemia treated in the single-UCB arm of the BMT CTN 0501 trial and recipients of a single UCB unit who appeared eligible without enrolling in the protocol and received trial (FluTBICy) and non-trial (TBI plus other agents or TBI-free) conditioning regimens[26]. As in our study, they reported that patients, whether or not included in the protocol, receiving FluTBICy conditioning had a better overall and leukemia-free survival after adjustment for risk factors. They also observed a decreased risk of relapse for patients undergoing TBI-based regimens compared to chemotherapy alone regimens (HR 1.61, 95% CI 1.06–2.42; $p = 0.02$). In a recent registry-based retrospective study analyzing MAC-UCB transplantation outcomes in adolescents and young adults with acute leukemia, Hayashi et al. also reported a reduced incidence of relapse after a TBI regimen, albeit not significant (24% and 35%, respectively, $p = 0.06$)[27].

Other explanations for the higher risk of relapse and subsequent lower DFS in the RW patients may be the lower incidence of chronic GvHD (19.8% vs. 51.3% in the randomized study, $p < 0.001$). The higher incidence of chronic GvHD reported in the RCT compared to most of the other published studies should be emphasized[16,27]. Due to the registry-based nature of the data of the RW group, we did not have detailed information on the severity of chronic GvHD for the patients in the RW group. Possible differences in minimal residual disease status, an unknown variable in both populations, might also explain the difference in the incidence of relapse between the RW and the RCT groups.

We conclude that the low transplantation strategy failure incidence observed in our RCT appears to be reproducible in children and young adults with acute leukemia in remission or myelodysplastic syndrome, transplanted with one or two UCB, provided that the nucleated cell dose is sufficient. The relapse incidence and DFS differences in ALL patients receiving different myeloablative conditioning regimens confirm the crucial role of TBI in the conditioning regimen and suggest the superiority of FluTBICy over other conditioning regimens.

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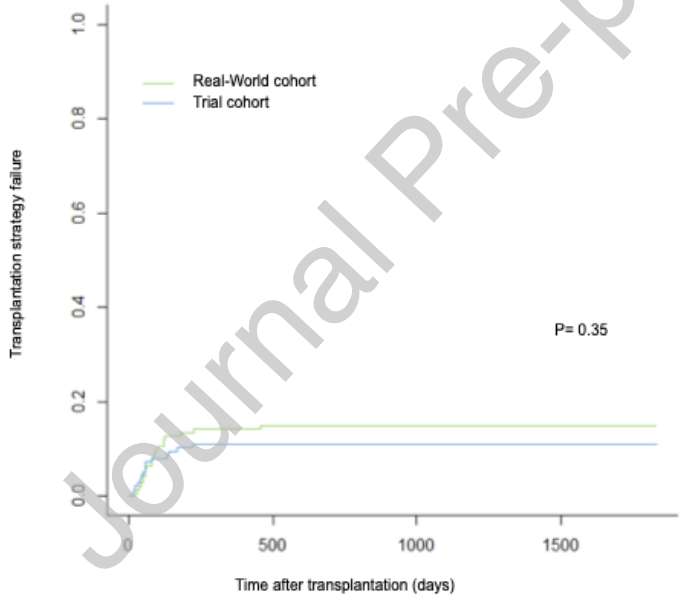


Figure 1. Cumulative incidence of transplantation failure.
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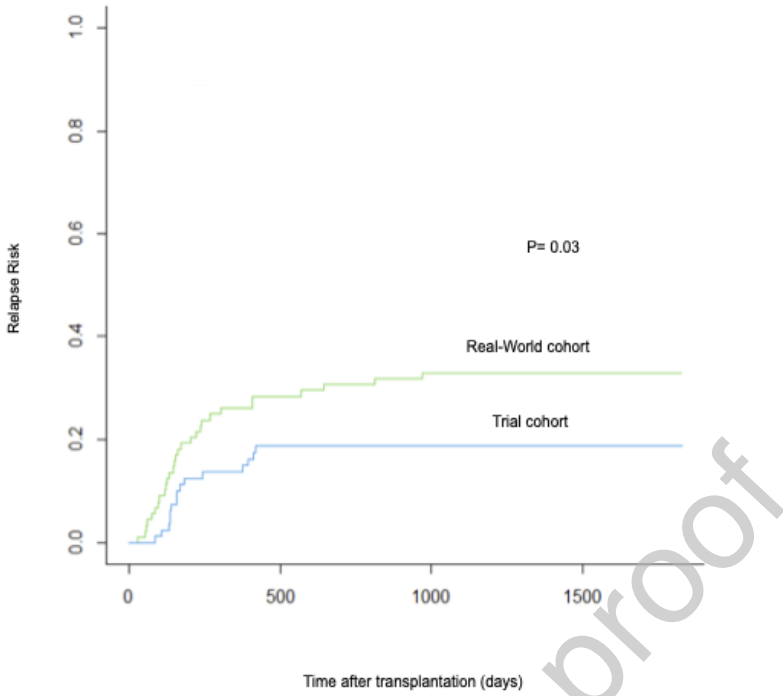


Figure 2. Cumulative incidence of post-transplantation relapse in ALL subgroup.

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Table 1
Patient, Disease and Transplantation Characteristics

	Trial cohort n = 137	Real-World cohort n = 141	P Value
Gender			0.25
Male	87 (63.5)	80 (56.7)	
Female	50 (36.5)	61 (43.3)	
Age at initial diagnosis, yr, mean (range)	9.55 (0.21 - 33.00)	8.23 (0.03 - 34.03)	0.17
Age at UCB transplantation, yr, mean (range)	11.15 (0.67 - 33.52)	9.86 (0.38 - 34.55)	0.18
Diagnosis			0.72
ALL	80 (58.4)	88 (62.4)	
AML	51 (37.2)	46 (32.6)	
MDS	6 (4.4)	7 (5.0)	
Disease status			0.85
CR1	68 (49.6)	68 (48.2)	
≥ CR2	63 (46.0)	66 (46.8)	
MDS	6 (4.4)	7 (4.0)	
Time from diagnosis to UCB transplantation, mo, mean (range)	19.2 (2.0 - 201.0)	19.0 (3.0 - 233.0)	0.95
Graft type			**< 0.001**
Single UCB transplantation	68 (49.6)	124 (87.9)	
Double UCB transplantation	69 (50.4)	17 (12.1)	
Follow-up duration from HSCT (days), mean (range)	798.0 (15.0 - 1,830.0)	752.0 (27.0 - 1,828.0)	0.46
Conditioning regimen			**< 0.001**
Cyclophosphamide + Fludarabine + TBI	83 (60.6)	43 (30.5)	
Busulfan + Cyclophosphamide	54 (39.4)	37 (26.2)	
Etoposide + TBI	0 (0.0)	12 (8.5)	
Thiotepa + Busulfan + Fludarabine	0 (0.0)	41 (29.1)	
Fludarabine + Busulfan	0 (0.0)	8 (5.7)	
TBI-containing regimen			**< 0.001**
No	54 (39.4)	86 (61.0)	
Yes	83 (60.6)	55 (39.0)	
Use of ATG			0.85
Yes	54 (39.4)	54 (38.3)	
No	83 (60.6)	87 (61.7)	
HLA compatibility			0.14
4/6	42 (30.7)	33 (23.4)	
5/6	81 (59.1)	73 (51.8)	
6/6	14 (10.2)	24 (17.0)	
Missing	0 (0.0)	11 (7.8)	

Data are presented as n(%) of patients, unless otherwise indicated.
CR, complete remission; TBI, total body irradiation; ATG, anti-thymocyte globulin.

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Table 2
TNC and CD34^{+} cell dose

	Trial cohort (1-unit UCBT, n = 68) (2-unit UCBT, n = 69)	Real-World cohort (1-unit UCBT, n = 124) (2-unit UCBT, n = 17)	P Value
Infused TNC (× 10^7/kg), median (range)			
1-unit UCBT	3.6 (1.0 - 15.2)	4.8 (0.12 - 34.9)	**0.031**
2-unit UCBT	7.3 (2.0 - 37.4)	4.3 (1.45 - 23.7)	**0.002**
Infused CD34+ cells (× 10^5/kg), median (range)			
1-unit UCBT	1.45 (0.16 - 10.6)	1.5 (0.2 - 12.3)	0.282
2-unit UCBT	2.6 (0.6 - 14.0)	1.5 (0.6 - 3.0)	**< 0.001**

TNC, total nucleated cells; UCBT, unrelated cord blood transplantation.

Size : 1 column

Table 3
Secondary endpoints: main post-transplantation outcomes

	Trial cohort n = 137	Real-World cohort n = 141	P Value
Two-year CI of Relapse	20.4% ± 6.8%	31.2% ± 7.7%	**0.01**
Two-year CI of TRM	8.8% ± 4.8%	7.8% ± 4.4%	0.74
Two-year Overall Survival	72.9% ± 7.8%	71.6% ± 7.6%	0.49
Two-year DFS	69.3% ± 8.0%	59.2% ± 8.4%	**0.047**

CI, cumulative incidence; TRM, transplant-related mortality; DFS, disease-free survival.

Size : 1 column

Table 4
Causes of death

Causes of death	Trial cohort n = 35	Real-World cohort n = 43
Relapse	23 (66%)	32 (74%)
Infection	6 (17%)	6 (14%)
Organ toxicity	3 (9%)	1 (2%)
GvHD	1 (3%)	3 (7%)
Other	2 (6%)	1 (2%)

Data are presented as n(%) of patients.
GvHD, graft-versus-host disease.

Size : 1 column

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