

Outcomes of unrelated cord blood transplants and allogeneic-related hematopoietic stem cell transplants in children with high-risk acute lymphocytic leukemia

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Summary:

Acute lymphocytic leukemia (ALL) is a common indication for hematopoietic stem cell transplantation (HSCT) in children. Use of unrelated cord blood (UCB) has become increasingly popular as a stem cell source, given the rapid availability and decreased GVHD potential. Publications describing outcomes of children with leukemia who underwent UCB transplants have compared them to those having received unrelated donor marrow transplants. Results are similar. We compared our outcomes using UCB vs allogeneic-related hematopoietic stem cells in pediatric ALL patients since 1992. A total of 49 patients were analyzed. All patients were either in CR1 with high-risk features ($n = 21$) or in CR2 ($n = 28$) with initial remission less than 36 months. Patients received myeloablation with fractionated total body irradiation, cyclophosphamide, and etoposide and GVHD prophylaxis with cyclosporine and methotrexate. Antithymocyte globulin was added for UCB recipients to address the HLA differences. In all, 23 patients underwent allogeneic-related HSCT and 26 underwent UCB transplantation. Other than increased time to engraftment for UCB recipients, results are equivalent. The 3-year overall survival is 64% and 3-year event-free survival is 60% for both groups. Rates of GVHD and transplant-related mortality are also equivalent. UCB is a reasonable option for children with ALL who are referred for HSCT.

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Although the majority of children with acute lymphocytic leukemia (ALL) enjoy excellent outcomes with conventional multiagent chemotherapy, the outlook for those patients who develop recurrent disease, particularly within the first 2 years of therapy, is far less favorable. Patients who relapse within 24 months of diagnosis and are treated with chemotherapy alone have less than 20% survival.^{1,2} Hematopoietic stem cell transplantation (HSCT) has been commonly employed for patients with relapse or high-risk features.^{3,4} While most children with recurrent or high-risk ALL can achieve a remission with intensified therapy, the most appropriate management strategy to employ once remission has been achieved remains controversial. Some transplant centers base that decision on whether a matched related donor is available.

For patients with relapse, HSCT with HLA-matched related donors during the second complete remission (CR2) has provided leukemia-free survival (LFS) rates in the range of 40–50% at 2–5 years.^{3,4} There exists controversy with regard to what length of time defines a late relapse after which point an HSCT may have no advantage over chemotherapy. In analyzing 287 patients with ALL in CR2, Uderzo reported no advantage of matched-sibling HSCT over chemotherapy for patients who relapsed more than 30 months from diagnosis.⁵ With unrelated cord blood transplantation (UCBT) for ALL and AML, a relapse on therapy prior to transplant confers a worse LFS (22% on therapy vs 48% off therapy).⁶

UCB can be an attractive alternative stem cell source for a variety of reasons. Cells are rapidly available, HLA-matching can be considerably less stringent than with unrelated adult bone marrow, and there is a lower incidence of acute and chronic GVHD. Furthermore, reports comparing UCBT to URD transplants suggest that outcomes are similar.⁷ Our data present a comparison of UCBT to traditional allogeneic-related transplants for children with high-risk ALL.

ALL patients considered for HSCT at our institution include: patients in CR2 who have relapsed (medullary or extramedullary) less than 36 months after diagnosis, patients in CR1 with high-risk features (unfavorable cytogenetics, age <1 year at diagnosis, and/or poor response to induction chemotherapy). The objective of this

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study was to compare outcomes in children with high-risk ALL (CR2 with remission <36 months and CR1 with high-risk features) who underwent either UCBT or allogeneic-related transplantation according to a standard protocol in a single institution.

Patients and methods

Patients

Beginning in 1992, a standard cytoreductive regimen was used for transplantation in patients with hematologic malignant disease regardless of the stem cell source. Prophylaxis of infections and GVHD was also comparable. Among patients enrolled in these studies, we confined the analysis described here to those with a diagnosis of B- or B-precursor ALL and high-risk features as described in Table 1. Requirements included age of 21 years or less, complete hematologic remission (histopathologic and cytogenetic analysis of bone marrow and cerebrospinal fluid) within 2 weeks of HSCT, and Lansky/Karnofsky performance status greater than 90. Pretransplantation evaluation of organs also needed to be satisfactory, with creatinine <1.5 times normal, bilirubin <1.5 times normal, AST and ALT both <2.5 times normal, shortening fraction >27% on echocardiogram, and FEV1 and FVC on pulmonary function testing >60%. For children who could not cooperate with pulmonary function tests, they needed to have a pulse oximetry >94% in room air with no evidence of dyspnea or exercise intolerance. Obviously there was a biologic, or genetic, selection of donor cells since allogeneic-related donors were used whenever available. Otherwise, patients received either UCBT or URD marrow transplant, depending on the availability and adequacy of donor cells. In general, at our institution, a patient without an HLA-identical sibling who has a UCB unit that has 2 or less HLA mismatches and a cell count greater than 4.0×10^7 TNC/kg⁸ will receive a UCBT instead of a URD marrow transplant. If multiple units with these characteristics are available, the one with the highest cell count is preferred. For purposes of this analysis, patients needed to have received stem cells from either UCB or an allogeneic-related source. A total of 49 patients satisfy these criteria and they are all included in this report. All transplant protocols are approved by the Children's Memorial Hospital IRB and either patients or their parents gave consent for transplant and associated therapeutic procedures and interventions.

Treatment

Patients received 150 cGy of total body irradiation for eight doses (total 1200 cGy) on days -9, -8, -7, and -6; etoposide at 1000 mg/m² as a continuous infusion on days -5 to -4; and cyclophosphamide (CY) at 60 mg/kg/day on days -4, -3, and -2 with MESNA prophylaxis. One patient, enrolled in a POG protocol, received cytarabine 100 mg/kg/dose every 12 h for 4 days instead of etoposide. From 1996 to 1999, UCBT recipients ($n = 12$) also received

one dose of thiotepa (TT) at 5 mg/kg on day -5. Patients with negative cerebrospinal fluid (CSF) cytology at all times prior to HSCT received an additional 600 cGy craniospinal boost if over 1 year of age or triple intrathecal therapy (methotrexate (MTX), hydrocortisone, cytarabine) monthly for 6 months after HSCT if under 1 year. The craniospinal boost was added to our standard protocol after two patients who had never had CNS leukemia relapsed in their CNS after HSCT. Patients with a history of positive CSF cytology at any time prior to HSCT received an additional 1200 cGy craniospinal boost prior to HSCT. All boys received an additional 400 cGy boost to the testes.

HLA typing was performed by serologic methods for class I antigens with confirmation of class II antigens by molecular analysis for all recipients and allogeneic-related donors. Hematopoietic stem cells were neither T-cell-depleted (in all but two parental graft cases) nor purged. Acute GVHD prophylaxis for allogeneic-related transplants consisted of cyclosporine (CSA) 1.5 mg/kg/dose i.v. every 12 h and MTX on days 1 (15 mg/m²), 3 (10 mg/m²), and 6 (10 mg/m²). CSA was changed to oral route once the patient was tolerating oral intake. UCBT recipients received continuous infusion CSA (5 mg/kg/day), which was changed to oral when tolerating oral intake, short-course MTX as above, and equine antithymocyte globulin (ATG: Upjohn, Columbus, OH, USA) at 20 mg/kg (premedicated with methylprednisolone 2 mg/kg/dose) on days 1, 3, 5, and 7. In the absence of GVHD, CSA was weaned at day 100, by about 10% per week, to have patients off CSA by day 180.

All patients were cared for in positive pressure laminar flow rooms. Additional supportive care included prophylactic fluconazole 3-5 mg/kg/day and acyclovir 250 mg/m² twice daily through day +180 and IVIG (250 mg/kg) or CMV immune globulin (100 mg/kg) (in the case of CMV-positive patient or donor) weekly until day +100, then monthly until 6 months after HSCT. Pentamidine (4 mg/kg i.v.) was given monthly for *Pneumocystis carinii* prophylaxis. Beginning in 1995, all patients received granulocyte colony-stimulating factor (G-CSF) at a dose of 5-10 μ g/kg starting at day +7. Broad-spectrum antibiotics were started empirically for febrile neutropenia. In general, for clinical grade II or greater acute GVHD, documented histologically, initial treatment was with methylprednisolone 2 mg/kg/day. Progression or no response after 1 week usually led to additional immunosuppressive therapy with agents such as ATG, infliximab or daclizumab, or switching calcineurin inhibitor. Acute GVHD was graded at least weekly according to the Keystone criteria and chronic GVHD was defined as limited or extensive.^{9,10}

Engraftment of neutrophils was defined as achievement of a peripheral neutrophil count above 500 cells/ μ l for 3 consecutive days. Engraftment of platelets was defined as a platelet count above 20 000/ μ l without transfusions for at least 7 days. Donor engraftment was determined by polymerase chain reaction assay of genomic DNA for variable-number tandem-repeat polymorphisms¹¹ after the year 2000 and by restriction-fragment length polymorphism (RFLP) before that period.

Statistical methods

Patient characteristics, including transplant and disease-related variables, were described using medians and frequencies for continuous and categorical variables, respectively. Since the sample size is relatively small, comparisons were made between UCBT and allogeneic-related transplant patients using nonparametric tests: Wilcoxon's test for continuous; and Fisher's exact test for categorical variables.

Duration of time for transplant-related outcomes used December 8, 2003 as date of last follow-up and hence observations are right-censored. Kaplan-Meier analysis was used to compare relapse, overall (OS) and event-free survival (EFS), and to obtain estimates of the median survival at 3 years. Days to neutrophil and platelet recovery are described using median and are compared using Wilcoxon's tests. The median neutrophil recovery was calculated for those patients recovering neutrophils by day 60 and median platelet recovery was calculated for those patients recovering platelets by day 180. Incidence of acute and chronic GVHD and proportion of early TRM are compared using Fisher's exact test. The effect of other patient characteristics (age, sex, HLA matching, unfavorable karyotype, infused cell dose, high-risk factors) along with transplant type on survival and EFS were investigated using Cox's proportional-hazards models. Age was dichotomized with the median age as the cutoff; complete HLA matching and presence of unfavorable karyotype and high-risk factors were also considered as binary indicators. The number of TNC cells infused was defined as whether or not it was below the median of the respective transplant group.

The data were complete and 5% was used as the level of significance. Statistical analyses were conducted using SAS and S-Plus.

Results

Patient and disease characteristics

Patient characteristics are seen in Table 1. Allogeneic-related transplant and UCBT recipients were very similar with respect to age, sex, high-risk features, and time to transplant. Overall, 57.1% of patients were in CR2 at the time of transplant, with the rest of the patients being high-risk CR1 patients. All the patients who underwent HSCT in CR2 had their relapse within 3 years from diagnosis. Two of these patients also had the t(4:11) translocation and one had the t(9:22) translocation. Patients who underwent HSCT in CR1 had several high-risk factors, including age less than 1 year at diagnosis ($n=13$), unfavorable karyotype ($n=16$), and poor response to induction therapy (induction failures) ($n=3$). Three infants had cytogenetics that were unknown or undeterminable. Unfavorable karyotypes for the patients in CR1 were t(9:22) ($n=7$), 11q23 ($n=4$), and t(4:11) ($n=5$). Among all patients, 17 had pretransplantation extramedullary disease (EMD) that involved the CNS ($n=14$), testes ($n=2$) and CNS and testes ($n=1$). Table 1 lists the combination of high-risk features for patients in CR1 by stem cell source received.

Graft/donor characteristics

Degree of HLA-matching can be seen in Table 1. Within the allogeneic-related cohort, all patients received matched-sibling donor transplants (one was syngeneic), except three who received a parental graft (5/6 HLA match with a class I mismatch). In two of these patients the graft was T-cell depleted (using selective depletion of CD8+ T-lymphocytes as described by Champlin *et al*¹²); there were no additional manipulations. Furthermore, within the allogeneic-related patients, all received stem cells from bone marrow collections, except three who received peripheral blood stem cells. Nucleated cell count and CD34+ cell count received were significantly higher in the allogeneic-related as opposed to the UCBT group.

Outcomes

On December 8, 2003, the median follow-up was 63 months (range 9–136 months). Since UCBT were only begun more recently at our institution, there was a significant difference in the follow-up durations for the two groups ($P=0.001$), with median follow-up of 38 months (10–105) for the UCBT group and 92 months (9–136) for the allogeneic-related group. The median year of transplantation was 2000 (1995–2003) for the UCBT group and 1996 (1992–2003) for the allogeneic-related group.

Early outcomes

Table 2 lists the proportions of patients with neutrophil and platelet recovery, acute and chronic GVHD, early transplant-related mortality (TRM), and probability of OS by transplant type. There was a significant delay of neutrophil ($P<0.0001$) and platelet ($P=0.011$) recovery in the UCBT group compared to the allogeneic-related group. The incidence of grade II–IV acute GVHD is equal in both groups. Furthermore, three patients in the allogeneic-related and two patients in the UCB group had grade III–IV acute GVHD. Early TRM was statistically equivalent in both groups (19% in the UCBT group and 13% in the allogeneic-related group ($P=0.71$)).

Late outcomes

The incidence of chronic GVHD was equivalent in both groups. Six UCB recipients and four allogeneic-related recipients had limited chronic GVHD, whereas one UCB recipient and four allogeneic-related recipients had extensive chronic GVHD. Nonadjusted estimates of 3-year OS and EFS are listed in Table 2 and shown in Figure 1. OS (64%) and EFS (60%) are similar in both groups. For both groups, all deaths prior to 100 days after HSCT were transplant-related and the majority of these were related to infection. After 100 days after HSCT, the majority of deaths in both groups were due to relapse.

Prognostic factors

Acute GVHD and chronic GVHD were not associated with a statistically significant difference in OS or EFS, in each group separately as well as in the whole group analyzed

Table 1 Patient, disease-related, and transplant characteristics of allogeneic-related transplant and UCBT for children with ALL

Characteristic	Allogeneic related (n = 23)	UCBT (n = 26)	P-value
Age at diagnosis (years)	2.5 (0.3–15.4)	3.9 (0.3–11.9)	0.63
Age <1 year	7 (30.4%)	6 (23.1%)	0.56
Age at transplant (years)	4.4 (0.5–15.7)	6 (0.6–14.9)	0.9
Sex (male)	13 (56.5%)	11 (42.3%)	0.32
Unfavorable karyotype	8 (34.8%)	11 (42.3%) ^a	0.79
Status at time of transplant (CR1)	11 (47.8%)	10 (38.5%)	0.34
High-risk factors for CR1 patients			0.79
Infants with t(4:11) or 11q23 (MLL)	5	3	
Infants with unknown cytogenetics	1	2	
Older than 12 mos, with t(4:11) or 11q23 (MLL)	0	1	
t(9:22)	3 ^b	4 ^c	
Poor response to induction	2	0	
<i>Extramedullary disease</i>			0.32
None	13 (57%)	19 (73%)	
At diagnosis	3 (13%)	1 (4%)	
Post diagnosis	7 (30%)	6 (23%)	
Time from 1st CR to relapse (days) ^d	(n = 12) 854 (336–1023)	(n = 16) 585 (218–1023)	0.23
Time from 2nd CR to transplant (days) ^d	(n = 12) 67 (53–120)	(n = 16) 87 (55–409)	0.11
<i>HLA disparity</i>			<0.001
0	20 (87%)	4 (15.4%)	
1 (A or B)	3 (13%)	10 (38.5%)	
2 (A and B)	0	8 (30.8%)	
2 (A or B and DRB1)	0	3 (11.5%)	
3 (A, B, and DRB1)	0	1 (3.8%)	
<i>CMV serostatus</i>			
Donor – → Recipient +	1 (4%)	4 (15%)	0.2
Donor + → Recipient –	4 (17%)	0 (0%)	0.03
Donor + → Recipient +	1 (4%)	0 (0%)	0.3
Nucleated cells infused (× 10 ⁸)	2.5 (0.6–4.5)	0.58 (0.12–1.6)	<0.001
CD34 (× 10 ⁶)	4.5 (1.4–21.3) ^e	0.62 (0.23–1.7)	<0.001

Data are represented either as frequency (percentage) or median (range).

P-values are obtained from χ^2 or Fisher's exact test for categorical variables and Wilcoxon's test for continuous variables.

^aThree patients with cytogenetic abnormalities underwent HSCT in CR2: two patients with the t(4:11) translocation and one patient with the t(9:22) translocation.

^bOne t(9:22) patient was also an infant.

^cOne t(9:22) patient also had poor response to induction.

^dFor patients undergoing HSCT in CR2.

^eMedian is 4.8 for the 18 patients who received unmanipulated bone marrow.

Table 2 Analysis of early and late outcomes after allogeneic-related transplant and UCBT for children with ALL

Outcome	Allogeneic related (n = 23)	UCBT (n = 26)	P-value
Neutrophil recovery at day 60	22 (96% (78–100))	23 (88% (80–98))	
Median days	15.5 (13–21)	29 (21–35)	<0.001
Platelet recovery at day 180	22 (96% (78–100))	20 (77% (56–91))	
Median days	24 (17–35)	51 (32.5–59)	0.011
TRM before day 100	3 (13% (3–34))	5 (19% (7–39))	0.71
Acute GVHD (grade 2–4)	5 (22% (7–44))	5 (19% (7–39))	0.83
Chronic GVHD ^a	8 (40% (19–64))	7 (33% (15–57))	0.66
Relapse-free at 3 years ^a	79% (57–100)	79% (61–98)	
Relapses	5 (25% (8.7–49))	4 (15% (4–42))	0.72
Survival at 3 years	64% (45–84)	65% (46–83)	
Deaths	9 (39% (20–61))	9 (35% (1–56))	0.74
EFS at 3 years	60% (40–80)	61% (42–80)	
Deaths and/or relapses	10 (43% (23–66))	10 (38% (20–59))	0.72

GVHD = graft-versus-host disease; TRM = transplant-related mortality; EFS = event-free survival.

^aPatients at risk: survivors after day 100.

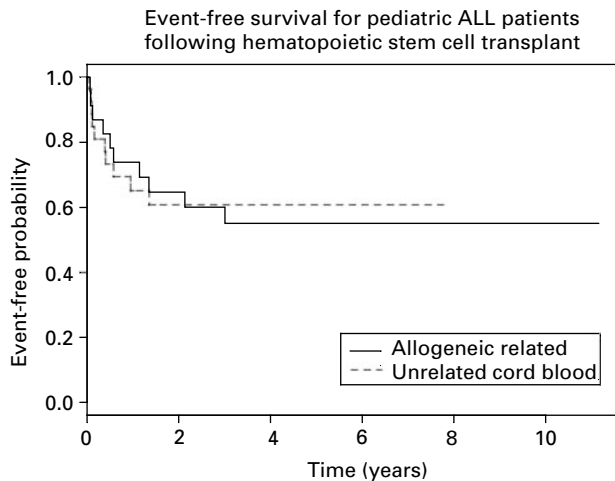


Figure 1 EFS for pediatric ALL patients following hematopoietic stem cell transplant.

together (data not shown). Cox's proportional-hazard regression was used to determine the effect of age (above or below the overall median age at transplant of 4.8 years), gender, presence of 1 or more risk factors, and degree of HLA matching on OS and EFS. None were significant; but there was a borderline association between gender (with females more likely to have a worse outcome) and both outcomes ($P=0.07$ OS, $P=0.08$ EFS) in the whole group. There was no statistical difference in outcome in CR1 vs CR2 patients. Furthermore, the effect of cell dose was examined by analyzing outcome within each group by using a dichotomized variable – above or below the median TNC/kg infused. There was no association between cell count and OS or EFS in either transplant group.

Outcomes of post-transplant relapse

Of the nine patients that relapsed, seven have died. None of those seven patients were able to achieve a stable remission after HSCT to be able to undergo a second HSCT. Both relapsed patients who remain alive are currently in remission. One had undergone allogeneic-related (syngeneic) transplant and one had undergone UCBT. The first patient is at high risk in that his original relapse was < 36 months from diagnosis; the second patient originally had the Philadelphia chromosome. Both patients achieved a stable remission with chemotherapy after their post-HSCT relapse. Both went on to receive second HSCT (the first with an HLA-matched unrelated donor, the second with a matched-sibling donor) with a reduced-intensity preparative regimen and both remain alive – the first patient 2 years and 2 months and the second patient eleven months following the second HSCT.

Discussion

The objective of our study was to retrospectively compare the outcome of transplantations for children with high-risk ALL at our institution using allogeneic-related marrow vs

UCB as a source of hematopoietic stem cells. We have shown that EFS and OS are comparable among the two groups of patients. The preparative regimen was the same in both groups. In addition, GVHD prophylaxis was the same (CSA with MTX), except that UCBT patients also received ATG. All patients in this study were considered to be at high risk, either because they relapsed less than 36 months from the first CR or because they had high-risk features at diagnosis. Furthermore, the patients in both transplant groups were very similar with regard to their age, CR1 vs CR2 status, degree of extramedullary disease, and number of high-risk factors. Patients in the UCBT group have had shorter median follow-up as cord blood units have only been more recently available as stem cell sources. The role of HSCT in ALL patients with high-risk features in CR1 has not been well defined. There does appear to be a survival advantage over chemotherapy using matched-sibling HSCT in this group of patients but this is solely based on single arm studies with 3-year LFS rates of 45–84%.^{13–15} High-risk features generally used to identify patients for HSCT in CR1 are age less than 1 year at diagnosis, poor risk cytogenetic findings, and poor response to induction.^{16–18}

The main differences pretransplant between the two groups relate to the graft characteristics. Most notably, within the UCBT group, most grafts were mismatched at one or two HLA alleles, with almost half of them being two allele mismatches. We are unable to say whether disparity at one specific allele confers better or worse outcome, but our data strongly confirm what other investigators have noted that umbilical cord has a different alloreactive potential than adult or even pediatric bone marrow.¹⁹ It appears that one can be much more permissive with HLA mismatches in the UCBT setting, although the benefit of lower GVHD may be offset by an increased risk of nonengraftment. Here, we have shown that the incidence of GVHD is comparable between mismatched UCBT and HLA-identical sibling transplants.

The main outcome difference between the two transplant groups was delayed neutrophil and platelet engraftment after UCBT. It is possible that the MTX and ATG may have further delayed engraftment. These agents have been standard GVHD prophylaxis for all alternative donor transplants at our center. It has been hypothesized that delayed engraftment in UCBT is due to the lower number of cells infused or to the immaturity of stem cells infused, which may take longer to differentiate into marrow progenitors.²⁰ Others have shown that a cord blood nucleated cell dose above $0.37 \times 10^8/\text{kg}$ was associated with an increased probability of engraftment.^{8,21} Our median nucleated cell dose for UCBT was $0.58 \times 10^8/\text{kg}$ and, within this group, median neutrophil and platelet engraftment was 29 and 51 days. This time to engraftment compares favorably with other published data.⁷ Given our sample size, we were unable to determine if within the UCBT group different cell doses infused yielded significant changes in time to engraftment. Furthermore, the delayed hematopoietic reconstitution in the UCBT group did not appear to adversely affect these patients, as the TRM was not statistically different when compared to the allogeneic-related group. It must be noted, however, that larger

samples of patients may lead to a statistically significant difference in TRM.

The incidence of acute and chronic GVHD was similar in both groups. This suggests that umbilical cord blood stem cells mismatched at ≤ 2 HLA loci have a similar alloreactive potential to HLA-matched siblings. Furthermore, rates of relapse were similar in both groups. Thus, our data indicate that there is no compromise in the graft-versus-leukemia effect using UCB as a source of stem cells. While more patients and longer follow-up are needed to confirm this observation, our data agree with previous reports noting that there is not an increased risk of leukemic relapse when using UCBT as a source of stem cells.⁷

In addition to similar rates of GVHD, rates of TRM were also similar among both groups. Most notably, the majority of deaths prior to day 100 after HSCT were related to infection. No deaths prior to day 100, in either group, were related to GVHD or recurrence. Our experience demonstrates that the increased time to neutrophil engraftment following UCBT did not translate into a significantly increased incidence of infection, although more patients are needed to confirm this observation. Our TRM rate for UCBT compares favorably to the data by Rocha *et al*⁷ and Dalle *et al*,²² where UCBT were compared to URD marrow transplants. This improvement may be due to our strategy (since 1998) of selecting UCB units with a high cell count as described above. It must be noted, however, that in a recent multicenter study of UCBT, cell dose lost significance as a prognostic indicator for TRM and survival when patient-related factors such as older age, female gender, and advanced disease were added to the multivariate model.²³

Interestingly, recent data have emerged suggesting that standard use of G-CSF increases TRM in leukemia patients who received matched-sibling marrow HSCT.²⁴ Whether our TRM in the allogeneic-related group would have been lower without the use of G-CSF remains to be answered by future studies. Furthermore, whether routine use of G-CSF adversely affects TRM in the UCBT recipient is unknown and therefore remains standard at this time.

Our data are not without limitations. First of all, these patients were not randomized to one group or another. All patients who had HLA-identical siblings received stem cells from their sibling source. If an HLA-identical sibling is not available, the team decides, among unrelated donors and UCB units, what source to use. Disease status, cell dose, HLA typing, viral status, and size of patient are taken into account when making this decision. While the patients were not randomized to one group or another, they are very similar in terms of their treatment and risk characteristics. Since a few years ago our data indicated equivalent results with UCBT as with matched-sibling transplants, the decision of whether to proceed with HSCT is based more on the patients and their disease and less on whether there is an allogeneic-related donor available or not. Furthermore, the issue of time trend could potentially be playing an effect. We have carried out UCBT only more recently so one could argue that the equivalent survival to matched-sibling transplants is due in part to improved supportive care. This is unlikely as our data span 10 years and other

than improved monitoring for CMV and adenovirus, supportive care has remained fairly constant. Additionally, follow-up is shorter within the UCBT group so there is a risk we may still see late relapses in these patients. However, the latest recurrence thus far was 19 months following UCBT. Finally, because of sample size, our analyses were limited to univariate comparisons not allowing us to adjust for other risk factors. There was also some heterogeneity in the stem cell products from related donors. Nonetheless, we feel our study indicates a trend towards equivalence in both arms and larger numbers of patients in each arm would be ideal to completely confirm our observations.

We conclude that for children with high-risk ALL in CR1 or children with ALL with initial remission less than 36 months in CR2, a UCBT provides equivalent long-term results when compared to the gold standard – a matched-sibling transplant. While the results are equivalent in both groups, they are not good enough. From this point forward, our efforts will be concentrated less on how to choose the perfect source of stem cells for each patient, and more on finding ways to achieve improved survival by lowering transplant-related toxicity and late effects. We are currently investigating the use of reduced-intensity HSCT (using either source of stem cells) for very high-risk pediatric ALL patients ($>CR3$ or organ damage). If such a regimen results in reduced TRM and late effects without increasing relapse rates or extensive chronic GVHD, we will increase the number of survivors of pediatric HSCT recipients and their quality of life.

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