



# Annotated Bibliography

## VII. Cord Blood Transplantation in Children



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### I. MALIGNANT DISORDERS

1. **Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukemia: a comparison study.** Eapen M, Rubinstein P, Zhang MJ, Stevens C, Kurtzberg J, Scaradavou A, Loberiza FR, Champlin RE, Klein JP, Horowitz MM, Wagner JE. *Lancet.* 2007;9;369(9577): 1947-54. [Abstract](#)

Allele-matched bone marrow is generally regarded as the preferred graft source. The aim of this study was to compare the leukemia-free survival after hematopoietic cell transplantation using allele-matched BMT and unrelated donor umbilical cord blood. These alternatives were compared utilizing present HLA-matching practices. The authors also assessed the relative effect of cell dose and HLA match, and their potential interaction on leukemia-free survival after cord-blood transplantation.

**Outcomes of 503 children (<16 years) with acute leukemia and transplanted with umbilical cord blood were compared with outcomes of 282 bone-marrow recipients.** All transplantation took place in the USA. Recipients of umbilical cord blood were transplanted with grafts that were HLA-matched (n=35) or HLA-mismatched for one (n=201) or two antigens (n=267) (typing at antigen level for HLA-A and HLA-B, and allele level for HLA-DRB1). Bone-marrow recipients were transplanted with grafts that were matched at the allele level for HLA-A, HLA-B, HLA-C, and HLA-DRB (n=116), or mismatched (n=166). The primary endpoint was 5-year leukemia-free survival.

**In comparison with allele-matched bone-marrow transplants, 5-year leukemia-free survival was similar to that after transplants of umbilical cord blood mismatched for either one or two antigens and possibly higher after transplants of HLA-matched umbilical cord blood.** Transplant-related mortality rates were higher after transplants of two-antigen HLA-mismatched umbilical cord blood (relative risk 2.31, p=0.0003) and possibly after one-antigen HLA-mismatched low-cell-dose umbilical-cord-blood transplants (1.88, p=0.0455). Relapse rates were lower after two-antigen HLA-mismatched umbilical-cord-blood transplants (0.54, p=0.0045). Treatment failure rates after transplantation of matched cord blood, one- or two-antigen mismatched cord blood and allele-mismatched bone marrow were similar to those of allele-matched bone marrow.

Interstitial pneumonitis and infections were frequent causes of early mortality after mismatched cord-blood transplants, but death from organ failure was more common after bone-marrow transplants than after cord-blood transplants. The proportions of early deaths due to recurrent leukemia and GVHD were similar in both groups.

**The authors interpreted these data to support the use of HLA-matched and one- or two-antigen HLA-mismatched umbilical cord blood in children with acute leukemia who need transplantation.** Because better HLA matching and higher cell doses significantly decrease the risk of transplant-related mortality after umbilical-cord-blood transplantation, greater investment in large-scale banking is needed to increase HLA diversity.

2. **Outcomes of transplantation in children with acute leukaemia.** Rocha V, Gluckman E. *Lancet.* 2007;369(9577):1906-1908. This article is a commentary on an article by Eapen et al. (*Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukemia: a comparison study.* *Lancet.* 2007;9;369(9577): 1947-1954) The Eapen article is posted above, [citation #1.](#)

Umbilical cord blood (UCB) has made allogeneic hematopoietic stem-cell transplantation available to patients who do not have an HLA-identical sibling or an unrelated donor. [*Comment: UCB transplants are also increasingly used even if a matched, unrelated donor is available, especially in children.*] **More than 10,000 cord blood transplants in children and adults have been performed for various genetic, hematological, or immunological disorders.**

The authors point out that even in children given an HLA allele-matched bone marrow unrelated graft (eight of eight), leukemia-free survival was not statistically significantly different from one or two HLA-mismatched umbilical cord blood transplantations compared with a HLA-allele-matched bone marrow, and that probably an HLA-matched recipient of umbilical cord blood had better outcomes than did an HLA-matched bone-marrow recipient. However, transplant-related mortality was increased in children transplanted with a low cord blood cell dose ( $<3 \times 10^7/\text{kg}$ ) and one HLA-mismatched cord blood graft, or in children given two HLA-mismatched cord blood transplants, independently of cell dose.

Therefore the recommended dose for choosing a cord blood unit should be more than  $3 \times 10^7$  nucleated cells per kg or more than  $2 \times 10^5$  CD34+ cells per kg. Additionally, the cell dose should be increased with the number of HLA mismatches. Cell dose should not be regarded as a limiting factor for cord blood graft acquisition, because of encouraging results of double cord blood transplantations and other efforts to improve engraftment. However, better HLA matching will only be possible by increasing the cord blood inventory and the quality of cord blood banked units.

3. **Strategies of the donor search for children with second CR ALL lacking a matched sibling donor.** Lanino E, Sacchi N, Peters C, Giardino S, Rocha V, Dini G; EBMT Paediatric, Acute Leukemia Working Parties; Eurocord. *Bone Marrow Transplant.* 2008 Jun;41 Suppl 2:S75-9. [Abstract](#)

During the last 10 years, the number of alternative haematopoietic stem cell transplantations (HSCTs) performed on children in

Europe has increased significantly and has reached 61% of the allografts. The authors provide practical guidelines to help define an algorithm for the treatment of children relapsing during or after first-line chemotherapy for ALL and lacking a matched sibling donor. The study focuses mainly on the effects of some factors, such as HLA matching, on survival in an effort to highlight the influence that these factors have on our choices.

**A simultaneous search for an unrelated donor and for a cord blood unit should be started. Although the availability of a well-matched donor is associated with improved overall survival, the major limiting factor for successful unrelated donor HSCT occurs when patients with rare phenotypes relapse while the search is still ongoing** (Also see *Category VI. Availability and time required to obtain cord blood versus bone marrow, citations 1, 2, 4, 5*) A less than two antigen mismatched cord blood unit containing more than  $3 \times 10^7$  nucleated cells should be considered equivalent to an 8/8 allele-matched unrelated donor. The decision should be made based on the urgency of the HSCT. Haploidentical HSCT should be offered if no donors and no cord blood units with acceptable characteristics are available.

4. **Searching for alternative hematopoietic stem cell donors for pediatric patients.** Rocha V, Locatelli F. Bone Marrow Transplant. 2008;41:207-14. [Abstract](#)

**The survival rates of unrelated donor HSCT refer only to patients who undergo transplantation and do not take into account those who did not find a donor.** The time needed to identify the right donor from a potential panel, to establish eligibility and to harvest the cells may, in patients who urgently need a transplant, favor the occurrence of leukemia relapse/progression, thus precluding the transplant feasibility, consequently, for patients who do not have a matched donor or who urgently need HSCT, attention has focused on umbilical cord blood transplantation and full haplotype-mismatched family members.

**Retrospective comparative studies.**

**UCBT compared to BMT from unrelated donors:** (1) Three published reports and a Eurocord registry analysis have concluded that the overall survival probability was not significantly different in UCBT or UBMT pediatric recipients, (2) A meta-analysis combining these comparative studies confirmed that there was no difference in 2-year overall survival between children given an unrelated UCBT or UBMT, (3) a more recent analysis compared results observed in 503 UCBT recipients with those of 282 UBMT recipients. In comparison with children given an allele-matched UBMT, patients transplanted with one or two HLA-disparate UCB unit had a similar 5-year disease free survival, while an even possible better outcome was evident for the 35 children given HLA-matched UCBT. (See *category VII Cord blood transplantation in Children, i Malignant disorders, Citation #1*)

**Comparison of UCBT with full haplotype disparate donor HSCT in children with ALL.** The Eurocord group in collaboration with the EBMT compared the outcome of patients given either UCBT or haplo-HSCT by performing a retrospective comparison of pediatric patients with high-risk ALL. There was no difference in terms of TRM and DFS.

5. **Indications and donor selections for allogeneic stem cell transplantation in children with hematologic malignancies.**

Handgretinger R, Kurtzberg J, Egeler RM. *Pediatr Clin North Am.* 2008;55:71-96. [Abstract](#)

This article provides a detailed review of the indications for stem cell transplantation in children with various hematologic malignancies. The authors provide a well organized and detailed review including 148 references, and the present article should be read in its entirety. Data regarding indications for transplantation are provided for patients (1) with high-risk features of ALL in first CR, (2) with relapsed ALL in second complete remission and beyond, (3) AML in first complete remission, (4) AML in second complete remission and beyond, (5) myelodysplastic syndromes, (6) juvenile myelomonocytic leukemia, (7) therapy-related myelodysplastic syndrome and AML and (8) CML.

Also, preparative regimens and donor selection for stem cell transplantation are reviewed. Regarding alternative-donor transplantations, the authors point out that a distinct advantage of unrelated donor UCB or haploidentical related donors is their rapid availability. A recent review of outcomes data reported to the CIBMTR showed that outcomes using 5 of 6 matched UCB donors were equivalent to those with matched bone marrow. (See *category VII Cord blood transplantation in Children, i Malignant disorders, Citation #1*)

6. **Indications and results of cord blood transplant in children with leukemia.** Gluckman E, Rocha V; EBMT Paediatric, Acute

Leukemia Working Parties; Eurocord. *Bone Marrow Transplant.* 2008 Jun;41 Suppl 2:S80-82. [Abstract](#)

The Eurocord registry has collected and analyzed data on unrelated cord blood transplants (UCBTs) performed in European Blood and Marrow Transplant Group (EBMT) and non-EBMT centers. **The literature shows that after UCBT relapse rate (RR), disease-free survival and overall survival of children with acute leukemia are similar to other hematopoietic stem cell sources (matched unrelated BM).** Disease status at the time of transplantation is found in several studies to be a very important determinant of long-term outcome.

The authors pointed out the following important facts about cord blood transplantation in children with leukemia:

The advantages of using cord blood are:

1. **The immediate availability of the donor.** This allows the transplant to be scheduled at the time of remission before the patient relapses. This is a considerable advantage in children with high-risk leukemia who need a transplant as early as possible after reaching remission.
2. The current consensus is to use any cord blood donor with 0-2 HLA differences and a number of nucleated cells  $3 \times 10^7/\text{kg}$ . **Therefore, it is now very rare to deny a transplant to a patient in need because of the lack of a donor.** (Note: *This is particularly true for Caucasians, but is less true for members of certain minority groups.*) In contrast, recommendations for an adult unrelated BMT where high-resolution typing must be performed for HLA-A, -C, DRB1, and -DQB1, the probability of finding a donor is approximately 50% and is strongly dependent on the ethnic origin of patients
3. The use of double cord blood transplants has overcome the problem of a low cell dose (in particular, for adults).
4. There is a decrease of GVHD while it seems that the GVL effect is observed.

The authors concluded that umbilical cord blood is a valuable alternative source of hematopoietic stem cell transplantation in children with acute leukemia who need an allogeneic transplant, but lack a suitable sibling donor.

7. **Is it time to expand the use of cord blood donor transplantation in relapsed ALL?** Kurtzberg J. *Pediatr Blood Cancer.*

2005;45:874-5. [Abstract](#)

This commentary is inspired by the publication of Sawczyn et al (see *citation # 8*, below). Although the majority of newly diagnosed children with ALL can be cured with standard chemotherapy, the treatment of patients with very high-risk disease or those who relapse remains both controversial and generally disappointing. Allogeneic transplantation is indicated for children

with very high-risk disease and for those who relapse on therapy and achieve a second remission. However, **for the patients lacking a matched-related donor, there is reluctance to refer for unrelated transplantation** until it is obvious that the patient cannot be cured with standard therapy alone.

Another obstacle to early transplantation is the belief that a matched unrelated adult donor is superior to a partially mismatched unrelated cord blood transplant. Often the search for a perfectly matched unrelated adult donor goes on for months and months during which time the child relapses and either is no longer a candidate for transplant or goes to transplant with a poorer prognosis.

The report by Sawczyn et al provides data on **26 consecutive children with high risk or relapsed ALL in 1<sup>st</sup>, 2<sup>nd</sup> or 3<sup>rd</sup> CR who were transplanted with partially mismatched unrelated donor umbilical cord blood (except one related transplant. After a median of 528 days, 62% of the children are surviving event-free.** In multivariate analysis, cell dose was the strongest predictor of survival. Patients receiving a low dose of UCB cells (<3 x 10<sup>7</sup> cells/kg) had dramatically lower EFS rates (15-20%) as compared to those receiving >3 x 10<sup>7</sup> cells/kg (>90% EFS [P = 0.007].

**These results are excellent for children with ALL undergoing allogeneic, unrelated transplantation.** The fact that only 4 of 20 evaluable children relapsed (20%) suggests that cord blood can confer a **graft-versus-leukemia effect** without intolerable GVHD.

**Since 1993, over 5,000 unrelated donor cord blood transplants have been performed world wide.** Knowledge about donor selection, preparative regimens, GVHD prophylaxis, and supportive care is expanding. **Given current results, pediatric oncologists treating children with high risk or relapsed ALL must think of referring their patients for unrelated donor cord blood transplantation earlier in the course of their disease when their chances for success are best.** Cord blood donors are readily available and easily procured. A donor unit can be made available within 1-2 weeks. Waiting for a closer HLA match or choosing a low cell dose donor to achieve a closer HLA match does not appear to be the best strategy.

8. **Cord blood transplant in childhood ALL.** Sawczyn KK, Quinones R, Malcolm J, Foreman N, Garrington T, Gore L, Gao D, Giller R. *Pediatr Blood Cancer.* 2005;45:964-70. [Abstract](#)

Allogeneic hematopoietic stem cell transplant (HSCT) has been used as a strategy to augment therapy for patients in initial remission (CR1) who are predicted to be at high risk of treatment failure if managed by chemotherapy alone, or for patients who have suffered relapses of their disease. A recent review of survival of patients with bone marrow relapses occurring within 3 years of initial diagnosis has suggested poor outcomes regardless of treatment strategy. Chemotherapy and matched unrelated donor (MUD) HSCT have had limited success in salvaging such patients. The former is limited by higher rates of relapse, whereas transplant-related mortality (TRM) compromises MUD HSCT outcomes. In addition, **there are limitations in donor availability with MUD HSCT due to the stringency of HLA-matching required between donor and recipient. Therefore, cord blood transplant (CBT) is being explored as a now widely available, alternative stem cell source.** In comparison to obtaining unrelated cord blood for HSCT, the donor identification process for MUD HSCT may be quite lengthy, extending time to transplant as a consequence. Increased interest in the use of CBT has prompted umbilical cord blood banks to be established worldwide and now there is a wide availability of donor products. **Since 1998, all cord blood donor searches for patients with ALL at the authors' institution have resulted in HSCT when clinically indicated.**

In this study, the authors evaluated **26 consecutive cord blood transplants (CBT) for ALL** performed using consistent conditioning therapy and graft-versus-host disease (GVHD) prophylaxis. Median patient age was 8.5 years (range, 0.5-24 year). Cord blood (CB) was from unrelated donors in 25/26 cases. Median CB nucleated cell dose was 3.26 x 10<sup>7</sup>/kg (range, 0.8-12.9). With median follow-up of 548 days, 16/26 patients (62%) are event-free survivors. Acute GVHD developed in 14/24 evaluable patients, reaching grade III-IV in 7 patients. Chronic GVHD occurred in 10/22 evaluable patients. Multivariate analysis showed higher total nucleated cell dose per kilogram to be the strongest predictor of event-free survival.

**The conclusion reached by the authors** was that their results suggest that CBT is an effective therapy for patients with high risk or recurrent ALL. The findings are more optimistic than much of the historically reported data, which are quite pessimistic regarding the potential for cure of high risk or refractory ALL by chemotherapy retreatment alone.

**When an HLA-matched sibling donor is unavailable, CBT may offer advantages over MUD HSCT as the preferred method of HSCT** because of the ability to accept lesser degrees of HLA-matching, consequent increase in available donors, and shorter time to HSCT. These encouraging results with respect to EFS using cord blood donors may derive from limited TRM while maintaining a low relapse rate.

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### I. MALIGNANT DISORDERS Page 2

9. **Total body irradiation, fludarabine, melphalan, and allogeneic hematopoietic stem cell transplantation for advanced pediatric hematologic malignancies.** Petropoulos D, Worth LL, Mullen CA, Madden R, Mahajan A, Choroszy M, Ha CS, Champlin RC, Chan KW. Bone Marrow Transplant. 2006; 37:463-7. [Abstract](#)

The authors evaluated the efficacy and toxicity of adding 9 Gy of total body irradiation (TBI), in three single daily fractions of 3 Gy, to the reduced intensity regimen of fludarabine 30 mg/m<sup>2</sup> i. v. x 4 days and melphalan 140 mg/m<sup>2</sup> i. v. x 1 day in advanced pediatric hematologic malignancies. **Twenty-two acute lymphoblastic leukemia (ALL), six acute myeloid leukemia (AML), and one non-Hodgkin lymphoma patients were transplanted.** Of these, 13 were beyond second remission, and five had prior hematopoietic stem cell transplant (HSCT). **Twenty-one donors were unrelated, of which 19 were from cord blood (CB) units.** Three of the eight related donors were genotypically disparate. Oral mucositis and diarrhea were the most common toxicities.

Twenty-seven patients achieved neutrophil engraftment (median 16 days), and 23 had platelet engraftment (median 42 days). One patient had primary graft failure. Seven patients died of non-relapse causes in the first 100 days. With a median follow-up of 52 months, seven of 22 ALL, five of six AML, and one of one lymphoma patients are alive and in remission.

**The authors concluded that the regimen of TBI, fludarabine, and melphalan allows the engraftment of allogeneic hematopoietic stem cells (including mismatched CB).** It was fairly well tolerated in pediatric patients, even for second transplants. Its efficacy requires further evaluation.

10. **Busulfan/Melphalan/Antithymocyte Globulin Followed by Unrelated Donor Cord Blood Transplantation for Treatment of Infant Leukemia and Leukemia in Young Children: The Cord Blood Transplantation Study (COBLT) Experience.** Wall DA, Carter SL, Kernan NA, Kapoor N, Kamani NR, Brochstein JA, Frangoul H, Goyal RK, Horan JT, Pietryga D, Wagner JE, Kurtzberg J. Biol Blood Marrow Transplant. 2005;11:637-46. [Abstract](#)

Although allogeneic transplantation offers potentially curative therapy to children and adults with otherwise untreatable malignancies, only a fraction of patients will have an HLA-matched donor in their family. Networks of unrelated volunteer donors have been established to provide an alternative donor source for those without family donors. However, with current HLA matching requirements, there remain a large proportion of patients for whom an unrelated volunteer donor is not identified in a timely fashion. Allogeneic transplantation from unrelated marrow donors is more frequently complicated by severe graft-versus-host disease (GVHD) or graft rejection.

Most prior studies with CBT have focused on total body irradiation (TBI)-based preparative regimens. There was interest in evaluating a non-TBI regimen for patients unable to tolerate TBI because of pretransplantation toxicity and leukemia patients <4 years of age. One stratum of the COBLT trial was to investigate the safety and efficacy of busulfan, melphalan, and antithymocyte globulin (ATG) as an alternative conditioning regimen to TBI.

**Thirty-eight patients with leukemia or myelodysplastic syndrome (MDS) were enrolled in the study.** The article presents the outcome of transplantations in the 32 children <4 years old who were enrolled on the trial. Within that subset, infant leukemia was defined as all cases diagnosed as leukemia before 6 months of age or diagnosed before 12 months of age with cytogenetic rearrangements carrying the mixed lineage leukemia gene.

The cumulative incidence (CINC) of neutrophil recovery (absolute neutrophil count >500/ $\mu$ L) at day 42 was 0.59 (95% confidence interval [CI], 0.44-0.78) at a median of 31 days (range, 23-55 days). The CINC and Kaplan-Meier estimates of platelet engraftment at day 180 were 0.53 (95% CI, 0.34-0.69) and 0.82 (95% CI, 0.61-1.00), respectively. CINC estimates of grade III/IV acute GVHD at day 100 and chronic GVHD at 1 year were 0.25 (95% CI, 0.09-0.41) and 0.26 (95% CI, 0.09-0.44), respectively. The CINC estimate of relapse was 0.31 (95% CI, 0.16-0.47) at 2 years. With a median follow-up of 27.8 months (range, 23.4-46.7 months), the probability of survival at 1 year was 0.47 (95% CI, 0.30-0.64).

The authors state that, in this small cohort, relapse and relapse-free survival were similar between patients in CR1 and those in CR2 and beyond. On the basis of current results with improved outcome in front-line chemotherapy and the reasonable salvage with CBT in CR2, **it is reasonable to consider CBT for infant acute leukemia in CR1 for those who are at high risk for relapse and who would be unlikely to enter a second remission should relapse occur. The benefit of CBT over a volunteer unrelated stem cell donor is that the time to donor identification is short, thus allowing transplantation immediately after reinduction/consolidation.**

*[Note: As an incidental finding, these authors found that high-resolution molecular HLA typing for HLA-A, -B, and -DRB1, performed in retrospect, correlated with improved survival. Such a finding is in apparent disagreement with the data presented by Kogler et al (See Annotated Bibliography IX, HLA matching, citation #5) who reported that high-resolution HLA typing by sequencing for HLA-A, -B, -C, -DR, -DQ in 122 unrelated cord blood/patient pair transplants hardly improves long-term clinical outcome.]*

11. **Outcomes of unrelated cord blood transplants and allogeneic-related hematopoietic stem cell transplants in children with**

**high-risk acute lymphocytic leukemia.** Jacobsohn DA, Hewlett B, Ranalli M, Seshadri R, Duerst R, Kletzel M. Bone Marrow Transplant. 2004;34:901-7. [Abstract](#)

The authors pointed out that, in publications describing outcomes of children with leukemia who underwent unrelated cord blood (UCB) transplants compared to results using unrelated donor marrow transplants, the results are similar. In this study, the authors compared 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). In all, 23 patients underwent allogeneic-related bone marrow transplants and 26 underwent UCB transplantation. Other than increased time to engraftment for the 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. The delayed hematopoietic reconstitution did not appear to adversely affect these patients, as the TRM was not statistically different when compared to the allogeneic-related transplants.

Notably, most UCB grafts were mismatched at one or two HLA alleles, with almost half of them being two allele mismatches. The median nucleated cell dose of UCB transplants was  $0.58 \times 10^8/\text{kg}$  and the median neutrophil and platelet engraftment was 29 and 51 days, respectively. The authors suggest that their favorable results may be due to the strategy (since 1988) of selecting UCB units with a high cell count.

The authors concluded that for children with high-risk ALL in CR1 or children with ALL with initial remission less than 36 months in CR2, an unrelated cord blood transplant provides equivalent long-term results when compared to the gold standard – a matched-sibling transplant.

*The policy at the authors' institution for patients without an HLA-identical sibling is that if there is a UCB unit that has 2 or fewer HLA mismatches and a cell count greater than  $4.0 \times 10^7$  TNC/kg, the patient will receive a UCB transplant instead of an unrelated donor marrow transplant.*

**12. Favorable Outcome for Infant Acute Lymphoblastic Leukemia after Hematopoietic Stem Cell Transplantation.** Jacobsohn DA, Hewlett B, Morgan E, Tse W, Duerst RE, Kletzel M. Biol Blood Marrow Transplant. 2005;11:999-1005. [Abstract](#)

**Infants with acute lymphoblastic leukemia (ALL) have a poor prognosis when treated with standard chemotherapy.** A subset of these infants, particularly those with mixed-lineage leukemia (MLL) rearrangements, has a high likelihood of relapse. **Hematopoietic stem cell transplantation (HSCT) performed early in first remission may improve outcome. This article presents results of 16 patients with infant ALL who were treated with HSCT in first remission.**

Six patients were  $\leq 6$  months of age at diagnosis, 11 had an initial white blood cell count of  $>50,000/\mu\text{L}$ , and all patients with determinable cytogenetics had a high-risk karyotype [t(4;11) abnormality or other MLL rearrangement]. All patients received 150 cGy of total body irradiation for 8 doses (1200 cGy). Fifteen of 16 patients received etoposide at  $1000 \text{ mg}/\text{m}^2$  as a continuous infusion over 24 hours and cyclophosphamide at  $60 \text{ mg}/\text{kg}/\text{d}$  for 3 days. **Eight patients received HSCT from an HLA-identical sibling, and 8 from unrelated cord blood.**

The HSCT was well tolerated; 15 patients achieved neutrophil engraftment at a median of 16 days. Two patients, one of whom had minimal residual disease at HSCT, died after relapse following HSCT. Two patients died of transplant-related causes (TRM = 12%). Other than these 2 deaths, there were no major complications, such as fungal infection or veno-occlusive disease. Twelve (75%) patients remain long-term survivors (median follow-up, 4.7 years). The fact that there were no late deaths suggests good immune reconstitution and minimal chronic GVHD.

More data are needed regarding the late sequelae after using TBI in infants. The risks and benefits, therefore, need to be clearly weighed before infants with ALL are submitted to HSCT. Nevertheless, it does seem that infants with very-high-risk leukemia, mainly those with *MLL* gene rearrangements, benefit from high-intensity allogeneic HSCT.

These results support the use of HSCT in the treatment of infant ALL, especially when used as consolidation in first remission. The risk of relapse seems to be decreased with this approach. Further work is being performed to determine the long-term effects from this therapy.

**13. Unrelated cord blood transplantation for childhood acute myeloid leukemia: a Eurocord group analysis.** Michel G, Rocha V, Chevret, et al. Blood 2003;102:4290-4297. [Abstract](#)

The authors reported results of unrelated cord blood transplantation in 95 children with AML (20 in CR1, 47 in CR2 and 28 in more advanced stage). Poor prognosis cytogenetic abnormalities were identified in 29 cases. Most patients had a 1 or 2 HLA antigen mismatched cord blood transplant. The median number of collected nucleated cells (NC) was  $5.2 \times 10^7/\text{kg}$ . Cumulative incidence of neutrophil recovery was  $78 \pm 4\%$ , acute GVHD was  $35 \pm 5\%$  and 100-day transplant-related mortality (TRM) was  $20 \pm 4\%$ . In multivariable analysis, a collected nucleated cell dose of higher than  $5.2 \times 10^7/\text{kg}$  was associated with a lower 100-day TRM. The two-year cumulative incidence of relapse was  $29 \pm 5\%$  and was associated with disease status. The 2-year leukemia free survival (LFS) was  $42 \pm 5\%$  ( $59 \pm 11\%$  in CR1,  $50 \pm 8\%$  in CR2, and  $21 \pm 9\%$  for children not in CR). Children with poor prognosis cytogenetic features had similar LFS to other patients. In CR2, LFS was not influenced by the length of CR1. The authors concluded that unrelated cord blood transplantation is a good therapeutic for children with very poor prognosis AML and who lack an HLA-identical sibling.

(NOTE: The median dose of nucleated cells "collected" ( $5.2 \times 10^7/\text{kg}$ ) seems generous and is likely to be an important factor regarding the good results obtained by these investigators. The median "infused" nucleated cell dose was  $4.4 \times 10^7/\text{kg}$ , indicating about 85% recovery of "collected" cells after processing, cryopreservation, and thawing. An important comment by the authors is that the TRM was  $17 \pm 5\%$  in transplants carried out after January 1998 whereas it was  $30 \pm 9\%$  before that date. Moreover, when the "collected" nucleated cell dose was above the median, the 100-day TRM decreased to  $9 \pm 4\%$ .)

In a commentary regarding this article (Blood 2003;102:4249), Dr. Przepiorka points out, "With intensive chemotherapy alone, children with AML who achieve a second remission following a long first remission have a prolonged survival, whereas those with a short first remission have a poor prognosis. In contrast, the good disease-free survival following unrelated donor cord-blood transplantation was independent of the duration of first remission. Moreover, a 2-year disease-free survival was 21% for children who underwent transplantation in relapse, a group with little chance of survival with chemotherapy alone. Thus, there appears to be a substantial graft-versus-leukemia effect with unrelated-donor cord-blood transplantation for patients with high-risk second remission and relapsed AML."

**14. Cord blood transplantation for children with acute leukaemia: a Eurocord registry analysis.** Gluckman E, Rocha V. Blood Cells Mol Dis. 2004;33:271-3. [Abstract](#)

This report provides results of unrelated cord blood transplants collected by Eurocord Registry in children with acute leukemia. **Children with AML:** 95 children were analyzed. The two year leukemia free survival was 42% in patients transplanted in first remission, 50% in second remission and 21% in children not in remission. Children with poor prognostic cytogenetic features had the same survival compared to other patients. **Children with ALL:** 195 patients with ALL were analyzed. The two year leukemia free survival was 36% in patients transplanted in remission and 15% in patients transplanted in relapse. **Results of unrelated cord blood transplants compared to unrelated bone marrow transplants in children with acute leukemia:** 416 children with acute leukemia received a HLA matched unrelated bone marrow transplant and were compared to 99 children transplanted with an unrelated HLA mismatched cord blood. The long term outcome between these groups were comparable with delayed engraftment in cord blood transplant, more relapse in T cell depleted bone marrow transplant and more GVH in the unmanipulated bone marrow transplant resulting in similar 5 years leukemia free survival.

The authors concluded that the results show that use of unrelated cord blood transplant is an option in patients lacking an HLA identical sibling donor.

15. **Survival after transplantation of unrelated donor umbilical cord blood is comparable to that of human leukocyte antigen-matched unrelated donor bone marrow: results of a matched-pair analysis.** Barker JN, Davies SM, DeFor T, Ramsay NK, Weisdorf DJ, Wagner JE. Blood 2001; 97:2957-2961. [Full Text](#)

A matched-pair analysis compared the outcomes of recipients of hematopoietic cell transplants using 0 to 3 HLA-mismatched cord bloods vs. HLA-A, -B, and DRB1-matched bone marrow as a source of stem cells. Patients were predominantly children (median age, 5 years) undergoing transplantation for malignancy, storage diseases, BM failure and immunodeficiency syndromes between 1991 and 1999. Although neutrophil recovery was significantly slower after cord blood transplantation, the probability of engraftment at day 45 was 88% in cord blood vs. 96% in BM-MTX recipients (n = 26 pairs), and 85% in cord blood vs. 90% in BM-TCD recipients (n = 31 pairs). The authors concluded that despite increased HLA disparity, probabilities of engraftment, GVHD, and survival after cord blood transplantation are comparable to those observed after HLA-matched marrow transplantation.

16. **Cord blood transplantation from HLA-mismatched unrelated donors as a treatment for children with haematological malignancies.** Ohnuma K, Isoyama K, Ikuta K, Toyoda Y, Nakamura J, Nakajima F, Tsuchida M, Ohira M, Suminoe A, Hara T, Nishihira H. Br J Haematol. 2001;112:981-987. [Abstract](#)

Factors influencing the outcome for 39 children with haematological malignancy who were subjected to a cord blood transplantation (CBT) from genotypically HLA-mismatched unrelated donors were analysed. This retrospective study included 21 children with acute lymphoblastic leukaemia, 15 with acute myelogenous leukaemia and one each with chronic myelogenous leukaemia, refractory anaemia with myelodysplastic syndrome (MDS) and juvenile myelomonocytic leukaemia (JMML). Those subjected to CBT during the first or second complete remission (CR) and MDS without blasts were assigned to the standard-risk (SR) group (n = 16). Patients in third or subsequent remission, relapse or partial remission with refractory leukaemia at the time of CBT were considered to be in advanced phase, and placed in the high-risk (HR) group (n = 11). JMML and the second CR after a relapse (n = 8), or bone marrow failure after a rejection (n = 3), following haematopoietic stem cell transplantation (HSCT) in the first CR were included in the high-risk group. Kaplan-Meier estimates for neutrophil and platelet recovery were 83.7 +/- 12.2 at d 60 and 55.4 +/- 16.6% at d 100 respectively. The incidence of grades II-VI acute graft-versus-host disease was 58.5 +/- 16.8%. The Kaplan-Meier estimate for 3-year event-free survival (EFS) was 49.2 +/- 16.6. From multivariate analysis, the most important factor influencing EFS was disease status at CBT: SR patients had a 3-year EFS of 75.0 +/- 21.6%, compared with 29.6 +/- 20.6% for those with HR disease (P = 0.013, RR 4.746, 95% CI 1.382-16.298). These data confirm that HLA-mismatched, unrelated CBT is a feasible procedure to cure a significant proportion of children with leukaemia, especially if conducted in a favourable phase of the disease.

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### I. MALIGNANT DISORDERS

17. (The following citation includes data on malignant and non-malignant disorders.) **Outcomes of unrelated cord blood transplantation in pediatric recipients.** Styczynski J, Cheung YK, Garvin J, Savage DG, Billote GB, Harrison L, Skerrett D, Wolownik K, Wischhoyer C, Hawks R, Bradley MB, Del Toro G, George D, Yamashiro D, van de Ven C, Cairo MS. Bone Marrow Transplant. 2004;34:129-36. [Abstract](#)

The authors report results of unrelated cord blood transplants (UCBT) in 29 pediatric recipients in one center from August 1997 to September 2002, and the risk factors associated with survival. The median age of the patients was 9 years (0.5-20); diagnoses were ALL, AML, CML, HD, HLH, NHL, NBL, B-thal, FA, FEL, Krabbe, WAS, SAA; the median follow-up was 11 months; conditioning was total body irradiation (TBI)-ablative (14), chemotherapy-ablative (6) and reduced intensity chemotherapy (9). The median total nucleated cell (TNC) dose was  $3.8 \times 10(7)/\text{kg}$  (1.1-11); median CD34+ :  $2.3 \times 10(5)/\text{kg}$  (0.2-9.9); and HLA match: 2 (6/6), 5 (5/6), 22 (4/6). The cumulative incidence estimate for neutrophil recovery at day +60 was 63%; two patients had neutrophil engraftment after day +60. Two patients had primary graft failure (2/23) (8.7%). Probability of  $\geq$ grade II aGVHD by day +60 was 27%,  $\geq$ grade III aGVHD was 20% and cGVHD 3%. Estimated 1-year overall survival (OS) 46% (95% CI 30-71) and for standard risk patients was 60% (95% CI 29-100%). Variables associated with improved survival by multivariate analysis include non-TBI-ablative conditioning (P=0.024), CD34+/kg (P=0.038) and gender (P=0.048).

The authors comment that their results indicating CD34 cell dose as a significant variable for hematopoietic reconstitution and for OS are complimentary to those of Wagner et al. The probability of aGVHD was strikingly lower than the results of less-HLA-disparate unrelated bone marrow transplants performed in children, and only one patient (cumulative incidence 3%) had extensive cGVHD. In comparison, cGVHD develops in 55-65% of patients receiving HLA-matched BMTs from unrelated donors. The authors suggest that the results should be viewed cautiously because of the small number of patients and events analyzed; the heterogeneity of the diagnoses, methods of conditioning and GVHD prophylaxis; and short follow-up.

18. **First report of autologous cord blood transplantation in the treatment of a child with leukemia.** Hayani A, Lampeter E, Viswanatha D, Morgan D, Salvi SN. Pediatrics. 2007; 119: e296-300. [Full Text](#)

The authors present the case of a 3-year-old girl with acute lymphoblastic leukemia who developed isolated central nervous system relapse while receiving chemotherapy 10 months after diagnosis. The child achieved a second remission on retreatment with systemic and intrathecal chemotherapy. She then underwent myeloablative chemotherapy and radiation therapy followed by infusion of her own umbilical cord blood, which the parents had saved after her delivery. Prior to transplantation, the authors used IgH receptor gene and T-? JG receptor gene loci rearrangements as molecular markers of the leukemia clone. The negative rearrangement signal in UCB, although positive in the leukemic bone marrow, gave the authors some assurance that the cord blood did not contain the leukemia clone. Given the sensitivity limitation of the standard PCR testing, however, one cannot completely rule out the possibility that a low-abundance leukemia clone was present in the UCB.

The patient is now doing well and is in complete remission 20 months after cord blood transplantation.

This report is apparently the first report of autologous CBT for the treatment of childhood leukemia. Autologous UCB transplantation has been reported in 1 patient with neuroblastoma and another with severe aplastic anemia.

In considering the choice of an autologous cord blood unit rather than an allogeneic unit, the authors state that the decision was based on the assessment that the benefits of decreased transplant-related mortality and morbidity (especially the ~30% chance of GVHD) in autologous CBT outweighed the risks of possibly reinfusing the leukemia clone to the patient, and the absence of graft-versus-leukemia effect.

The authors add a disclaimer stating that it is not their intention in this report to advocate private UCB collection and its use but, rather, to report an isolated case and discuss some of the issues and uncertainties surrounding this procedure.

*[Comment: The authors do not comment on the fact that the recurrence rate after autologous transplantation for leukemia is significantly higher than the recurrence rate after allogeneic transplantation and, as a result, overall survival is higher after allogeneic HSCT. The authors do not comment on whether a matched allogeneic unit was available but, instead, point out that they considered an autologous unit to be preferable. ]*

19. **Outcomes of unrelated umbilical cord blood transplantation in pediatric patients with myelodysplastic syndrome.** Parikh SH, Martin PL, Szabolcs P, et al. Biol Blood and Marrow Transplant 2005;11(2, Suppl 1);80.

The authors point out that myelodysplastic syndromes (MDS) in children are associated with significant risk of leukemic transformation. Thirty children with MDS were transplanted with unrelated umbilical cord blood. Median age was 9.06 years and median weight was 28.4 kg. Eight patients had secondary MDS and 10 patients had bone marrow blasts  $>20\%$ . The preparative regimen was TBI-based in 19 and chemotherapy-based in 11 patients. Grafts delivered a median of  $4.12 \times 10^7$  nucleated cells/kg precryopreservation, and the median CD34+ cell dose infused postthaw was  $1.48 \times 10^5/\text{kg}$ . Median time to ANC  $>500/\mu\text{L}$  was 24 days and median time to platelet recovery ( $>50\text{K}$  untransfused) was 72 days. aGVHD grade III-IV occurred in 5 patients; limited

cGVHD was seen in 4 patients.

Fifteen patients (50%) died and 15 are surviving in remission from 3.4 to 107 months (median, 50 months) posttransplantation. Six of 8 children with secondary MDS (75%) are alive compared to 13 of 22 (40%) with primary MDS, possibly due to the greater number of patients with >20% blasts in the latter group. These results, especially in patients with <20% blasts pretransplantation, are equivalent to matched allogeneic bone marrow transplantation data.

20. **Allogeneic hematopoietic cell transplantation for infants with acute lymphoblastic leukemia.** Sanders JE, Im HJ, Hoffmeister PA, Gooley TA, Woolfrey AE, Carpenter PA, Andrews RG, Bryant EM, Appelbaum FR. *Blood* 2005;105:3749-3756.

**Abstract**

The authors state that the role of transplantation in infants with acute lymphoblastic leukemia (ALL) is not defined. Accordingly, they analyzed results of 40 infants diagnosed before age 12 months who received a hematopoietic cell transplant (HCT) between July 1982 and February 2003 in CR1 (n=17), CR2/3 (n=7) or relapse (n=16). Patients were conditioned with cyclophosphamide with total body irradiation (n=39) or busulfan (n=1). Hematopoietic cell grafts included unmanipulated bone marrow from 24 related and 13 unrelated donors, peripheral blood stem cells from 1 unrelated donor and **cord blood from 2 unrelated donors**. Graft-versus-host disease (GVHD) prophylaxis was methotrexate or cyclosporine (7) or methotrexate plus cyclosporine (33). Thirty-nine engrafted, 20 developed acute GVHD, and 7 chronic GVHD. Sixteen relapsed and seven died of other causes. Patients in CR1 had disease-free survival (DFS) of 76% compared to 45% for CR2/CR3 and 8% for relapse (P=0.0001). Of 33 patients with cytogenetic data, 26 (79%) had MLL gene rearrangement. Fourteen of these 26 were in CR1 and 11 survive in remission. Outcome was associated with phase of disease, but having the MLL gene was not a factor predictive of outcome. Late effects included growth and other hormone deficiencies. The investigators concluded that their data demonstrate that infants with ALL and MLL gene have excellent DFS when transplanted in CR1 and consideration for transplantation in CR1 is warranted.

21. **Unrelated cord blood transplantation for children with high risk myelodysplastic syndromes.** Alessandra Picardi, Domenico Del Principe, Laura Cudillo, Teresa Dentamaro, Sergio Amadori and Paolo de Fabritiis. *Haematologica* 2004;89(5):ELT08 ([e-letter](#))

The authors assessed the feasibility and toxicity of unrelated mismatched cord blood transplant in five pediatric patients with high-risk myelodysplastic syndrome. Four patients were at high-risk according to the FAB criteria and one because of age > 2 years, hemoglobin F level greater than 10%, low platelet count, associated immunodeficiency and hemolytic anemia. Before transplantation, two children were treated with chemotherapy: one failed 2 chemotherapy-induction cycles and one had a failure and disease progression after 1 locus mismatched allogeneic transplant from the mother.

Although all patients were considered at high risk of relapse because the proportion of marrow blasts ranged from 12% to 25% at transplant, full donor chimerism was achieved in 4/5 cases on day 28 and two patients are in continuous complete remission more than 5 years after no evidence of cGVHD.

On the basis of their study, the authors state that a search for an unrelated donor, including umbilical cord blood, should be mandatory for patients with MDS who lack an HLA-identical sibling, particularly in pediatric patients who have a longer life expectancy than adults.

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