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Transplant Outcomes in Acute Leukemia (I)

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Abstract

Umbilical cord blood (UCB) has gradually emerged over the last decade as an alternative source of hematopoietic cells for transplantation in children and adults with high-risk or advanced hematological malignancies who do not have a suitably matched related or unrelated adult donor. This increase in use of UCB is due to favorable results in children, growing availability of UCB units with large cell doses, less stringent donor-recipient HLA matching and rapid identification and acquisition of the unit. In children with acute leukemia, the data support similar leukemia-free survival after transplantation of HLA-matched and 1 or 2 HLA-mismatched UCB and HLA-matched unrelated donor bone marrow. In adults with acute leukemia, some reports suggest a survival advantage after transplantation of matched unrelated bone marrow compared to UCB and others, similar leukemia-free survival. Work is in progress to improve hematopoietic recovery and lower early transplant-related deaths, the two major limitations to a successful outcome after UCB transplant. The importance of HLA-matching and cell dose on outcomes after UCB transplantation support the need for an even greater investment in public cord blood banks. Simultaneously searching of accredited cord blood banks and bone marrow donor registries for patients without an HLA-matched sibling thought to benefit from hematopoietic stem cell transplantation is encouraged.

Overview of hematopoietic stem cell transplant

Selecting an appropriately matched donor for hematopoietic stem cell transplantation (HSCT) and the patient's disease status at transplantation are important determinants of success. The optimal donor is an HLA-matched sibling. In the absence of such as a donor, unrelated donor transplantation from a suitably matched volunteer adult donor or umbilical cord blood is acceptable. HLA matching at HLA-A, -B, -C and -DRB1 (8/8 match) between unrelated adult donors and recipients has been associated with best survival.¹ In that report, a single mismatch at the HLA-DQ locus when donor and recipient were matched at HLA-A, -B, -C, -DRB1 was not associated with adverse outcomes. Donor-recipient mismatches at HLA-B or -C appear to be better tolerated than were mismatches at HLA-A or -DRB1 for bone marrow (BM) transplantation.¹ As with BM transplants, 8/8 match between unrelated adult donors and recipients is associated with best survival after peripheral blood progenitor cell (PBPC) transplants and mismatches at HLA-A, -B or -DRB1 were better tolerated than at HLA-C.² In

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both reports^{1,2}, mortality risks were similar comparing low-resolution (antigen) versus high-resolution (allele) mismatches, except for HLA-C, where allele-level mismatches were not associated with mortality. The effect of HLA-mismatch on mortality was most evident when transplantation occurred in first complete remission with an absolute difference of 9-10% in overall survival after matched and single mismatched transplants.¹ For patients with more advanced disease, this difference was considerably lower at 3-5% implying disease status at transplantation is also an important determinant of survival after HSCT.¹

It is generally accepted that UCB does not require the same rigor of HLA-matching as BM or PBPC from unrelated adult donors. In a recent analysis of the National Marrow Donor Program's donor registry, the probabilities of finding an 8/8 matched unrelated adult donor were 51% for Caucasians, 30% for Hispanics, 20% for Asians and 17% for African Americans (M. Maier, personal communication, August 2008). Consequently, use of UCB increases access to HSCT, particularly for ethnic minorities for whom identifying a suitably matched unrelated adult donor has been difficult. Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) indicate UCB now accounts for approximately 40% of unrelated donor transplantations in children and 10% in adults.

A prospective randomized clinical trial is the accepted standard to compare different treatment regimens. However, there have been no prospective trials comparing transplantation of UCB to BM or PBPC and none are planned. The feasibility and acceptability of such a clinical trial are problematic. Few have suitably matched volunteer adult donors and randomization of these persons to receive BM or mismatched UCB is unlikely to be acceptable to most patients and physicians, as the current standards are to use an 8/8 unrelated adult donor when such a donor is available. Consequently, reports comparing transplant outcomes after unrelated adult donor and UCB transplantation have utilized data collected by the large observational registries like the CIBMTR and the European Group for Blood and Marrow Transplantation (EBMT).

Hematopoietic recovery

Transplantation of matched or mismatched BM in children with leukemia results in hematopoietic recovery in most recipients. and the cumulative probability of recovery higher than after transplantation of UCB.^{3,4} Recovery rates after transplantation of UCB in children with leukemia vary with cell dose.^{3,4} Most reports show lower recovery rates after transplantation of mismatched UCB units containing cryopreserved total nucleated cells (TNC) $\leq 3 \times 10^7$ /kg of recipient weight. Others have identified CD34 doses above which hematopoietic recovery after transplantation of UCB is superior compared to transplantation of units containing a lower dose.^{5,6} In the report by Wagner and colleagues⁵ UCB units containing a minimum of 1.7×10^5 CD34 cells/kg were more likely to achieve myeloid engraftment. Wagner and colleagues demonstrated a positive correlation of CD34 dose with TNC ($r=0.55$, $p<0.01$).⁵ van Heeckeren and colleagues⁶ also report higher myeloid engraftment after infusion of UCB units with $\geq 1.2 \times 10^5$ CD34 cells/kg. It is not surprising the optimal CD34 dose is different in the above mentioned reports. Methods of CD34 analysis vary between institutions and this has prevented the establishment of a universally acceptable threshold value which can be used by transplant centers for UCB unit selection. To-date none of the studies in adults with leukemia comparing transplantation of BM to UCB have shown an effect of TNC on hematopoietic recovery.^{7,8} As seen with children, recovery rates are significantly lower after transplantation of UCB, likely because most adult recipients receive units containing the minimum required or a slightly higher TNC, which does not all for determination of an optimal dose in these individuals. It is assumed that doses of TNC and/or CD34 doses identified in children can be adhered to when selecting a UCB unit for adults. In recent years, the banking and selection of UCB units with large TNC and transplantation of two UCB units to achieve the required TNC have been predicted to yield hematopoietic recovery rates comparable to those after

transplantation of BM or PBPC. Gluckman and Rocha⁹ have also suggested hematopoietic recovery is influenced by HLA disparity in addition to TNC and the negative effect of HLA disparity may be abrogated by transplantation of cryopreserved units containing $>3 \times 10^7/\text{kg}$ TNC. Such an effect was most apparent with transplantation of 1-locus mismatched UCB units in children and absent when the disparity was >2 .

Graft-versus-host disease

Risks of acute graft-versus-host disease (GVHD) vary with recipient age at transplantation and donor-recipient HLA disparity. In a recent analysis of children with acute leukemia in North America, risks of grade 2-4 acute GVHD were lower after transplantation of matched UCB (6/6 matched) compared to matched BM (8/8 matched), with relative risk (RR) 0.45, 95% CI 0.22 – 0.96, $p=0.039$.⁴ However, risks of grade 2-4 acute GVHD were similar after transplantation of 1- or 2-antigen mismatched UCB and matched BM.⁴ These observations differ from an earlier report from the Eurocord-Registry.³ In that experience, risks of grade 2-4 acute GVHD were lower after transplantation of matched or mismatched UCB compared to matched or mismatched BM. The observed difference between the North American and European reports may be explained by the inclusion of matched and mismatched BM recipients as a single group and HLA matching of BM donors and recipients considered low resolution typing at HLA-A and -B and no consideration of matching at HLA-C locus in the European report. Among adult recipients of mismatched UCB grafts, the Europeans observed similar risks of grade 2-4 acute GVHD (RR 0.81, 95% CI 0.59 – 1.10, $p=0.17$)⁸ as the North American report, lower risks (RR 0.57, 95% CI 0.37 – 0.87, $p=0.01$)⁷ compared to matched BM transplants (6/6 match). Acute GVHD risks were lower after transplantation of mismatched UCB compared to mismatched BM (RR 0.66, 95% CI 0.44 – 0.99, $p=0.04$).⁷ In Japan, risks of acute GVHD were lower after transplantation of UCB compared to 8/8 matched BM (RR 0.61, 95% CI 0.39 – 0.95, $p=0.028$);¹⁰ likely explanation the observed differences in acute GVHD risks in the Japanese population is the relative homogeneity of the study population.¹¹

Overall, the risk of developing chronic GVHD is lower after UCB transplantation compared to BM (considering HLA-matching at HLA-A, -B, -DRB1) in children with leukemia.³ However, comparing chronic GVHD after matched BM (8/8 matched) to matched and mismatched UCB transplantation, the risks were similar.⁴ As observed with risks of acute GVHD after BM and UCB transplantation in adults in some reports has suggest similar risks of chronic GVHD, and in other publications, a lower risk of developing chronic GVHD after transplantation of matched BM.^{7,8} In the general experience, the severity of chronic GVHD after UCB transplantation has been limited in the majority of affected individuals.^{7,8}

Transplant-related mortality

Transplant-related mortality is an important determinant of survival after HSCT. This outcome is particularly relevant for recipients of UCB transplantation, due to slower myeloid recovery than after BM transplantation and recovery determined in part by TNC of the unit and donor-recipient HLA disparity. In children with acute leukemia, transplantation of UCB units mismatched at 1-antigen and precryopreserved TNC $>3 \times 10^7/\text{kg}$ improved early survival, such that the risk of transplant-related mortality is similar to that after transplantation of 8/8 matched BM (RR 1.48, 95% CI 0.89 – 2.46, $p=0.133$).⁴ When precryopreserved TNC is $\leq 3 \times 10^7/\text{kg}$, mortality risks are higher (RR 1.88, 95% CI 1.01 – 3.47, $p=0.046$) and most events occur early (within 3-6 months after transplantation). Transplant-related mortality risks are higher after transplantation of 2-antigen mismatched UCB unit compared to 8/8 matched BM (RR 2.31, 95% CI 1.47 – 3.62, $p<0.001$).⁴ An optimal TNC dose above which early survival is better was not identified. Most units contained precryopreserved TNC $2.5 - 4.0 \times 10^7/\text{kg}$ and a higher

TNC may be required (if feasible) to overcome the negative effect of mismatching at 2-antigens.

In adult recipients of 1 or 2-antigen mismatched UCB transplant, a TNC dose above which early survival is similar to that after matched BM has not been described.^{7,8} Most adult recipient UCB transplants are mismatched at 2-antigen and in recent years UCB units containing higher TNC doses ($2.5 - 4 \times 10^7/\text{kg}$ precryopreserved) are used for transplantation. This combination of factors has led to the practice of transplanting two UCB units instead of one to achieve the desired TNC. Although there has never been a formal comparison of use of two versus one UCB unit for transplantation, transplant-related mortality rates appear to be low with transplantation of two UCB units.^{12,13} The transplant conditioning regimen is “reduced intensity” for the majority of these transplants and only a formal comparison of patients undergoing double UCB transplant to those undergoing BM or PBPC transplants with similar intensity transplant conditioning regimens can determine whether risks of transplant-related mortality differ.

Leukemia recurrence

In children, one report demonstrated lower leukemia recurrence after transplantation of UCB mismatched at 2-antigens compared to 8/8 matched BM (RR 0.54, 95% CI 0.36 – 0.83, $p=0.005$).⁴ The observed lower risk of recurrence was further examined by comparing transplant related mortality and recurrence risks in children alive at 6- and 12-months after transplantation, in order to ensure the risk of recurrence was not due to the higher early transplant related mortality (and fewer children alive at a later period at risk to experience leukemia recurrence). Transplant related mortality risks were similar at 6 months and beyond 12 months after 2-antigen mismatched UCB transplants and 8/8 matched BM, and recurrence rates were lower after 2-antigen mismatched UCB transplant than after 8/8 matched BM (RR 0.50, $p=0.005$ and RR 0.41, $p<0.001$ at 6- and beyond 12-months, respectively). None of the published reports in adults comparing transplantation of UCB to that after BM have shown a significant difference in leukemia recurrence.^{7,8}

Leukemia-free survival

The Eurocord Registry – EBMT showed similar risks of treatment failure (leukemia recurrence or death from any cause; inverse of leukemia-free survival) after transplantation of UCB and BM for adults with acute leukemia.⁸ In contrast, the North America summary showed higher treatment failure after transplantation of UCB mismatched at 1- or 2-antigens as compared to 6/6 matched BM in adults with acute and chronic leukemia (RR 1.48, 95% CI 1.18 – 1.86, $p=0.001$; Figure 1).⁷ Patient selection varied: the Europeans excluded patients with chronic leukemia and included prior recipients of autologous transplants whereas as the Americans included patients with chronic leukemia and excluded those who had received an autologous transplant prior to the unrelated HSCT.

Children with acute leukemia from Europe and North America show similar risks of treatment failure after transplantation of 1- or 2-antigen mismatched UCB and matched BM (considering matching at HLA-A, -B, DRB1)³ and at HLA-A, -B, -C, -DRB1, Figure 2.4 Transplantation of 6/6 matched UCB ($n=35$) led to higher 5-year leukemia-free survival compared to matched BM; 60% vs. 38%, respectively, RR 0.54, 95% CI 0.30 – 0.97, $p=0.041$.⁴ While promising, the relatively small sample size upon which this observation is based requires the results to be validated in a larger cohort of patients. Treatment failure (inverse of leukemia-free survival) after transplantation of 1-antigen mismatched high cell dose UCB (RR 0.94, 95% CI 0.71 – 1.75, $p=0.730$), 1-antigen mismatched low cell dose UCB (RR 1.12, 95% CI 0.68 – 1.31, $p=0.634$) and 2-antigen mismatched UCB (RR 1.17, 95% CI 0.87 – 1.57, $p=0.297$) were similar compared to 8/8 matched BM. The observed higher leukemia-free survival after matched UCB,

if confirmed in a larger population, would alter current donor selection such that when a UCB unit is 6/6 matched to the patient with precryopreserved TNC $>3 \times 10^7/\text{kg}$, UCB would be the donor source of choice in preference to an unrelated adult donor matched to the patient (8/8 match) as in current practice.

The data presented here favor transplantation of matched or mismatched UCB for children and adults with acute leukemia when an 8/8 matched adult donor is not available or when transplantation is needed urgently, as for most patients with acute leukemia who achieve a second complete remission. The high early transplant related mortality after mismatched UCB transplant is a limitation, and strategies to lower the higher early mortality are currently being investigated. In addition to transplantation of two UCB units and safer transplant preparative therapies,^{12,13} other strategies being investigated to lower early mortality include co-infusion of mesenchymal cells, co-infusion of T-cell depleted haploidentical peripheral blood, ex-vivo expansion culture of cord blood hematopoietic stem cells and improved homing.¹⁴⁻¹⁶ Further, in adults with leukemia, PBPC is the predominant graft used accounting for about 70% of unrelated donor HSCT. With the increasing use of PBPC grafts comparing transplant related mortality and leukemia-free survival after transplantation of PBPC to UCB grafts are underway. We know chronic graft-versus-host disease rates are high after transplantation of PBPC from unrelated donors¹⁷ and they may affect long-term survival in good risk patients as has been shown to occur after HLA-matched sibling donor transplantation.¹⁸

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Figure 1. Probability of leukemia-free survival after bone marrow and cord blood transplantation adjusted for disease status at transplantation. Reproduced from the New England Journal of Medicine, 2004, vol 351, 2265-2275

Figure 2. Probability of leukemia-free survival after bone marrow and cord blood transplantation adjusted for disease status at transplantation. Reproduced from the Lancet, 2007, vol 369, 1937-1954