Annotated Bibliography

VI. Availability and Time Required to Obtain Cord Blood Versus Bone Marrow

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1. **Results of an unrelated transplant search strategy using partially HLA-mismatched cord blood as an immediate alternative to HLA-matched bone marrow**. Dalle JH, Duval M, Moghrabi A, Wagner E, Vachon MF, Barrette S, Bernstein M, Champagne J, David M, Demers J, Rousseau P, Winikoff R, Champagne MA. Bone Marrow Transplant. 2004;33:605-11. Abstract

   Approximately one-third of the patients in need of an unrelated transplant do not have a suitable graft identified if the search is restricted to HLA-matched bone marrow (BM). The authors report the results of a strategy accepting unrelated cord blood (CB) as an immediate first-line alternative to BM in children in need of an unrelated transplantation.

   Search for an unrelated donor was initiated in 91 patients. Absence of mismatch was required for adult donors, and up to two mismatches were allowed for CB grafts, with a nucleated cell dose over 2.5 x 10^7 cells/kg before thawing. In six cases, donor search was eventually cancelled because of patient death. Five of these deaths occurred during the first month of search. An unrelated graft was identified within 3 months for 84 patients of the 85 remaining patients *(94% of the patients transplanted in this study were Caucasian)*. Among those, 64 were transplanted, 36 with CB and 28 with BM. The remaining **20 patients were not transplanted, due to disease evolution**. The time from decision to transplantation was 1 month shorter for CB. Survival of the 36 patients transplanted with CB was similar to that of the 28 patients transplanted with BM. The 3-year survival was 59% in CB and 57% in BM patients.

   In summary, the authors suggest that their results strongly support the use of unrelated CB in children as an **immediate alternative** to unrelated BM transplantation if there is no BM donor readily available. A similar survival when CB is chosen early, together with more rapid availability of CB, suggest that unrelated **CB transplantation may be considered as a choice equivalent to that of unrelated BM transplantation**.

2. **How to improve the search for an unrelated haematopoietic stem cell donor. Faster is better than more!** Heemskerk MB, van Walraven SM, Cornelissen JJ, Barge RM, Bredius RG, Egeler RM, Tj Lie JL, Revesz T, Sintnicolaas K, Wulffraat NM, Donker AE, Hoogerbrugge PM, van Rood JJ, Claas FH, Oudshoorn M. Bone Marrow Transplant. 2005;35:645-52. Abstract

   Although there are over 8 million available stem cell donors in registries, it is still true that a significant percentage of patients worldwide in need of a hematopoietic stem cell transplantation do not receive a graft. To determine the reasons for this, the authors analyzed 549 searches for Dutch patients.

   Between 1996 and 2000, 59% of the patients of Northwest European origin received a graft from an unrelated donor (UD),11% of the patients lacked a compatible donor, and 30% became medically unfit for transplantation. This is in contrast to the patients of non-Northwest European origin for whom UD shortage is still the most important impediment; only 32% were transplanted while 50% lacked a compatible donor.

   Two main causes that led to failure to reach transplantation were identified: (1) either no acceptable donor was available, or (2) the patients' clinical condition deteriorated to a point that stem cell transplantation was no longer an option (in these cases failure to find a donor was not the primary impediment).

   Only a small group of patients of Northwest European origin with rare HLA phenotypes could not be transplanted due to a lack of an acceptable donor. In spite of the increased search efficiency, the percentage of patients of Northwest European origin who became medically unfit to proceed with transplantation remained around 30% throughout the study.

   The urgency status as assessed by the clinicians failed to identify the majority of the patients with a rapidly declining clinical condition. As it seems difficult to predict which patients need a graft most urgently, **it seems important to shorten the UD search time interval to transplantation for every patient in need of a stem cell transplantation**. Also, precious time is lost on the waiting list of some transplant centers.

   In contrast to the recruitment of Northwest European donors, the recruitment of new donors of non-Northwest European origin should be actively pursued and efforts to collect cord blood units from non-Northwest Europeans should be encouraged.

   The authors conclude that their data suggest that the most efficient way to increase the percentage of patients of Northwest European origin reaching transplantation is to **decrease the time spent on the whole process** and to increase the level of HLA typing of the donors at the registries to allele level. In addition, they propose an enlargement of the availability of cord blood units from non-Northwest Europeans.

   (Comment: The importance of the fact that cord bloods can be obtained rapidly in comparison to marrow or peripheral blood stem cell products has been underestimated. This study points out that a major cause of not proceeding to transplant was deterioration of the clinical condition while awaiting transplant. Others have reached a similar conclusion, as indicated in the citations below.)

3. **Assessment of optimal size and composition of the U.S. National Registry of hematopoietic stem cell donors**. Kollman C, Abella E, Baitty RL, Beatty PG, Chakraborty R, Christiansen CL, Hartzman RJ, Hurley CK, Milford E, Nyman JA, Smith TJ, Switzer GE, Wada RK, Setterholm M. Transplantation. 2004;15;78:89-95. Abstract

   The authors determined likelihoods of finding an HLA-A,B,DRB1 matched donor for patients of various racial/ethnic groups from the NMDP registry. In 2002 the likelihood of finding a matched donor listed in the registry was 40% for blacks, 56% for Asian/Pacific

Islanders, 79% for whites and 57% for Hispanics. The authors comment that donor unavailability considerably reduces the likelihood of finding a donor. Incorporating the problem of unavailable donors into the calculations, the estimates were 27% for blacks, 45% for Asian/Pacific Islanders, 75% for whites and 48% for Hispanics. If recruitment is maintained at its current level, then the likelihoods of finding an available donor by 2007 are projected to increase to 34% for blacks, 54% for Asian/Pacific Islanders, 79% for whites and 55% for Hispanics.

Scenarios under which minority recruitment is increased by either 15% or doubled from its current rate show relatively little additional improvement in the projected matching probabilities. For example, doubling the rate of new black volunteers would only change the projected probability of an available HLA-matched donor for patients of that race from 34% to 37%, and would have negligible impact on other racial/ethnic groups.

The authors point out that the number of patients currently searching the NMDP Registry and proceeding to transplant is considerably smaller than what might be expected on the basis of the rate of sibling-donor transplantation. (For comment about this important point, go to the left column of the Home Page and click on Interactive Forums, Medical Professionals, *The unrealized potential of umbilical cord blood (UCB) units for unrelated donor hematopoietic cell transplantation*.)

Registries of cord blood units can provide adequate matches for a large majority of patients. (For more information see citations #4, 5 and 6 below.

4. **Searching for unrelated donor hematopoietic stem cells: availability and speed of umbilical cord blood versus bone marrow.** Barker JN, Krepski TP, DeFor TE, Davies SM, Wagner JE, Weisdorf DJ. Biol Blood Marrow Transplant 2002; 8:257-260. Abstract

   Of 171 consecutive referrals for unrelated donor transplantation, 108 proceeded to a formal search with selection of at least 1 donor. At least one 4-6/6 HLA-antigen matched umbilical cord but no suitable bone marrow graft was identified for 21 of the 108 patients (19%). *The median time required to obtain a bone marrow donor was 49 days compared to a cord blood search time of only 13.5 days*. Faster availability is a particular advantage for patients requiring urgent transplantation.

   Two of the authors (JNB and JEW) point out that, at the University of Minnesota, if the transplant is deemed urgent (that is, required within 3 months of referral), a strong preference is given to cord blood, provided that a unit with greater than 2.0 x 10^7 cells/kg can be identified. (Barker JN, Wagner JE. Umbilical-cord blood transplantation for the treatment of cancer. Nat Rev Cancer 2003; 3:526-532.)

5. **Impact of marrow unrelated donor search duration on outcome of children with acute lymphoblastic leukemia in second remission.** Dini G, Valsecchi MG, Micalizzi C, Busca A, Balduzzi A, Arcese W et al. Bone Marrow Transplant 2003; 32:325-331. Abstract

   The authors analyzed the outcome of 167 children with second CR acute lymphoblastic leukemia, for whom an unrelated donor search was activated. A suitable donor was identified for 70 patients, but *a further leukemia relapse occurred during the search in 94 children at a median of 4 months after search activation*, 36 of whom underwent a transplant beyond second CR while 58 died of progressive disease. The outcome data showed that relapse is the major limiting factor for unrelated donor BMT in children with ALL in second CR after a bone marrow relapse. They suggested that unrelated donor and cord blood searches should be initiated during the first CR in patients at high risk for relapse.

6. **Results of an unrelated transplant search strategy using partially HLA-mismatched cord blood as an immediate alternative to HLA-matched bone marrow**. Dalle JH, Duval M, Moghrabi A, et al. Bone Marrow Transplant. 2004;33:605-11. Abstract

   The authors suggest that the impact of including cord blood (CB) in the initial strategy of unrelated graft search in a cohort of patients has been the object of limited analysis. They report the results of such a strategy in 91 consecutive children. Absence of mismatch was required for adult donors, and up to two mismatches were allowed for CB grafts, with a nucleated cell dose over 2.5 x 10^7 TNC/kg. A graft was found for 84 of the 85 children who remained available for a 3-month search. In all, 64 patients were transplanted, 36 with CB and 28 with bone marrow (BM). Primary graft failure, acute grade II-IV and extensive chronic graft-versus-host disease occurred in five, five and zero CB, and in three, one and two BM patients, respectively. The 3-year survival was 59% in CB and 57% in BM patients. The authors concluded that **accepting CB as a source of stem cells offers a graft to almost every child in need of an unrelated transplantation, with a probability of survival similar to that of unrelated BM transplantation.**

7. **Non-HLA barriers to unrelated donor stem cell transplantation.** Kollman C, Weis T, Switzer GE, Halet M, Kitajima D, Hegland J et al. Bone Marrow Transplant 2001; 27:581-587. Abstract

   A prospective survey involving 544 searches of the US National Marrow Donor Program (NMDP) Registry was conducted to identify reasons why many patients who have apparent HLA-matched donors do not proceed to transplant. Coordinators at NMDP transplant centers, patients and referring physicians were surveyed shortly after the initial search, and follow-up surveys were sent to the coordinators as the search was ongoing. The death of the patient, worsening of the patient's medical condition and *length of the search process were the most commonly cited barriers to transplantation*. Other times a decision was made not to transplant through the NMDP due to the use of a donor from another source, a preference for chemotherapy or immunotherapy, hesitancy on the part of the transplant physician or patient, or because the patient did not require a transplant.

8. **The importance of identifying a back-up donor for unrelated stem cell transplantation**. van Walraven SM, Heemskerk MB, Lie JL, Barge RM, Cornelissen JJ, Egeler RM, Verdonck LF, Wulffraat N, Oudshoorn M. Bone Marrow Transplant. 2005;35:437-40. Abstract

   Transplant centers erroneously count on the unrelated volunteer donors to be willing, available and medically fit for actual donation. According to the authors' data, which includes 502 unrelated donor work-up procedures performed for 425 Dutch patients between 1987 and 2002, one of 11 work-ups ended in the primary requested donor failing to donate. In cases for which a back-up donor was already identified, the patients were transplanted with a delay of less then 2 weeks; **when no back-up donor was available, the median delay increased to 18 weeks**. The necessity for second unrelated donor search not only incurs search costs but also costs of extra treatment and hospital admission for the patient. Another aspect is the time that is needed to perform a second unrelated donor search. A number of patients will be at risk of relapse or deterioration of their disease, and will therefore no longer be eligible for stem cell transplantation if there is an untimely delay to transplantation due to donor deferral.

   *(Comment: The authors do not comment on the fact that **the above problem is not an issue with cord blood units**. There is no concern about unavailability once a unit has been identified. Also, efficient cord blood banks can release a unit within 24 hours of request, once the optimal unit has been identified. Thus, this report illustrates a significant advantage of using cord blood units, although it is not mentioned by the authors.)*

9. **Ability of minority patients to find donors from an ethnically diverse cord blood bank**. Baxter-Lowe LA, Kim Y, Carter S, et al.

Blood 2002;100:640a-641a.

Of 7,662 units in the cord blood transplantation (COBLT) bank, 43% were from Caucasian donors, 22% Hispanic, 15% African American, 8% Asian and 12% mixed/other/unknown. In 481 searches, approximately 45% non-Caucasian, using intermediate resolution typing at HLA Class 1A and B and high resolution typing at DRB1, *93% of patients were able to identify a unit delivering a minimum of 1 X 10^7 cells/kg matching at a minimum of 4/6 HLA loci (44% 5/6 or 6/6)*. The authors concluded that cord blood donors could be identified for diverse patient populations.

10. **Availability of unrelated donors for hematopoietic stem cell transplantation for hemoglobinopathies**. Krishnamurti L, Abel S, Maiers M, Flesch S. Bone Marrow Transplant 2003; 31:547-550.

    The NMDP maintains a registry of 4 million volunteer donors, and facilitates unrelated donor transplants. Donor searches were run in April 2001 for a cohort of 272 thalassemia patients and 77 sickle cell disease patients in order to determine the likelihood of finding a potential donor. About 59.7% of sickle cell patients and 80.2% of thalassemia patients will find at least one potential 6/6 HLA matched donor or umbilical cord blood unit. When the search is extended to include 5/6 HLA-matched bone marrow, or 4/6 HLA-matched cord blood donors, at least on potential donor will be identified for all patients.
    NOTE: The authors do not comment on the fact that many (perhaps 50%) of registered donors are not available when requested to donate, a problem that does not exist after locating a cord blood for transplantation.

11. **Racial/ethnic diversity achieved in national network of cord blood banks**. Ballen KK, Kurtzberg J, Lane TA, et al. Blood 2002;100:186a

    Of 6,725 cord blood units that have been banked, HLA typed and available for transplant in the American Red Cross Cord Blood Program, 32% are from non-Caucasian donors; 11% African American, 12% Hispanic, 4% Asian, 1% Native American, and 3% other. The authors concluded that a racially diverse group of cord blood units can be obtained in a national network.

12. **Second cord blood transplantation (CBT) with reduced-intensity conditioning for graft failure after the first CBT for AML.** Ohwada C, Nakaseko C, Ozawa S, Takeuchi M, Shono K, Koizumi M, Sakaida E, Cho R, Saito Y, Nishimura M. Bone Marrow Transplant. 2004;34:999-1000.

    The authors state that there are few data on the management of graft failure after cord blood transplantation (CBT) as CBT is a relatively new procedure. They provide the first report of a patient with graft failure after CBT who was successfully treated with a second CBT with reduced-intensity conditioning.

    A 16 year old girl with AML failed to achieve remission with the first three courses of induction chemotherapy and finally reached CR after the fourth course. She received a CBT using a two HLA- mismatched unrelated cord blood containing 2.27 x 10^7 TNC/kg after a conditioning regimen consisting of CY and TBI. No hematologic recovery was observed through day 30. A second transplant was performed following a reduced intensity conditioning regimen consisting of Flu, busulfan, and ATG; tacrolimus was started on day -1 for GVHD prophylaxis. On day 43 of the initial transplant, a three-HLA-loci mismatched cord blood containing 4.42 x 10^7 TNC/kg was transplanted. On day 21, the patient's ANC rose above 500/mm^3 and engraftment was achieved with complete donor chimerism. She developed *de novo* type extensive chronic GVHD with mild liver damage and sicca syndrome. She remains in CR 19 months after the second CBT, although currently suffers from refractory CMV retinitis.

    The authors comment that prompt availability and less stringent requirements for HLA identity make cord bloods a feasible source of stem cells for a second transplant following graft failure. They add that the use of ATG may increase the risk for viral infection after transplantation, which may have been of significance in this patient.

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