

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Cord Blood Transplants

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H&O What are the challenges in finding a matched blood unit from an unrelated donor?

MD The stem cell transplant is actually a simple procedure: it is a transfusion which the patients receive intravenously. The difficult part is identifying the right donor.

The process of searching for an unrelated bone marrow donor relies on the extensive inventory that is procured and mediated by the National Marrow Donor Program (NMDP). Its registry—now called the “Be The Match” Registry—has access to over 7 million donors and nearly 90,000 cord blood units world wide. Although this is a large number, the probability of finding a matching donor within the registry is dictated by the patient’s race and/or ethnic origin. For example, if the patient is Caucasian, the likelihood of finding a bone marrow donor is very high. However, if the patient is African-American, the likelihood is significantly less. The probabilities for those who are of Vietnamese, Indian, or Hispanic ethnicity are also very low. Asians, with the exception of the Japanese, are also an underrepresented race in the registry (Japan has a very strong and highly efficient registry of donors).

There are 2 reasons for the difference in racial variability in the NMDP inventory. First of all, several countries have lower degrees of registry development, and their populations will therefore be underrepresented. Secondly, genetic heterogeneity poses a problem. Especially in the United States, those who are African-American or His-

panic are extremely heterogeneous in terms of genetics, which make it intrinsically more difficult to find donors for these patient populations. A patient can be from Spain and of Caucasian background, or another from Central America with an American Indian background. With a history of repeated migration, it becomes much more complicated with these heterogenic populations.

In general, the process of identifying a donor is based on a histocompatibility test (the human leukocyte antigen [HLA]). HLA matches represent a degree of compatibility between a donor and a recipient.

The basic standard matching criteria for a bone marrow transplant from an unrelated donor is in 5 genes: HLA-A, -B, -C, -DRB1, and -DQ. There is one collection of genes that one receives from his or her mother and another collection from his or her father (a haplotype), which adds up to 10 genes. An acceptable bone marrow donor is matched in 9 of 10 genes or 10 of 10 genes. A 10 of 10 is considered the gold standard for bone marrow transplantation from an unrelated donor. The more mismatches there are, the greater the likelihood of graft-versus-host disease (GVHD) and the poorer immunologic recovery the recipient will experience after the transplant. Other complications such as cell dysfunction (eg, not producing platelets) may follow. The most feared complication of allogeneic transplantation, however, which increases with HLA mismatches, is GVHD, where donor lymphocytes identify cells in the patient’s body as foreign and attack them.

H&O What are the advantages of cord blood transplants that bone marrow transplants do not have?

MD The main benefit with cord blood transplants is that a much higher degree of mismatch is tolerated compared to bone marrow transplants. Today, in order to identify a matched donor for cord blood transplants, we look at 3 genes: HLA-A, -B, and -DRB1. With one set of genes from each mother and father, a person will have 6 markers to consider; currently, those who match 4 of the 6 markers or more with the patient are acceptable cord blood units for transplantation. Consequently, the cord blood donor pool dramatically increases because more mismatches are allowed. This development has the potential to greatly impact the treatment of patients who cannot find donors (ie, minorities).

Cord blood is very rich in hematopoietic stem cells. Proportionally, it is much richer than bone marrow and peripheral blood. These hematopoietic stem cells can potentially form healthy blood in recipients. The other potential advantage of cord blood is that the immune cord blood cells are more naive than those in the bone marrow. Therefore, cord blood causes a less serious GVHD.

Close relatives, especially brothers and sisters, are more likely than unrelated people to be HLA-matched. However, families today are shrinking, and there is an increasing number of families with only one child. This issue is becoming more pressing because more families with less children translates to less possible donors in the family. Therefore, the issue of an unrelated donor transplant and transplants outside the family is a social concern. For example, many families in China have no more than one child. Thus, they have a paucity of related donors. When they are in need of a bone marrow transplant, they will need to use unrelated bone marrow or cord blood transplants, or mismatched related donors.

H&O Are there statistical differences in success rates between bone marrow transplants and cord blood transplants?

MD There are no randomized trials comparing bone marrow and cord blood transplants. Most cord blood transplant studies have been retrospective and registry-based or from single institutions. However, I believe we can summarize the difference as follows: bone marrow or peripheral blood stem cell transplant will give you faster engraftment. In general, transplant recipients receive chemotherapy or radiation to immunosuppress

their bone marrow. Their blood counts will go down, and the time it will take for them to recover will depend on the cell dose given. Because bone marrow and peripheral blood stem cells can be given in higher cell doses, patients recover their blood counts and immune system faster. However, those transplants are more associated with GVHD than cord blood transplants.

In contrast, patients who receive a cord blood transplant will less likely experience GVHD, but it will take longer for the new blood stem cells to produce white cells, red cells, and platelets. The reason behind this trade-off is a significantly lower cell dose contained in a single unit of cord blood compared with a bone marrow or peripheral blood graft. Therefore, adult recipients of cord blood transplantation will always take longer to produce blood than adult recipients of a good bone marrow transplant. For the same reason, there is also a higher rejection rate for cord blood transplants. Also, in some patients, the cord blood cells are accepted but do not produce platelets.

For a pediatric recipient, however, cord blood transplants provide a relatively higher cell dose, given the difference in size, for example, between a baby versus a grown adult. It is much easier to engraft a 2-month old baby than a 7-foot tall person with the same number of cells. In some instances, cord blood transplantation has now been proposed to replace bone marrow transplantation.

H&O In what type of scenarios would cord blood transplantation be suitable?

MD For the reasons mentioned above, smaller adults and pediatric patients would benefit from this procedure. For fully grown adults transplants, cord blood is currently not considered the general stem cell source of choice. However, if an adult patient without a donor in the family is in need of a transplant, there are institutions that may move straight to cord blood transplants for the following 2 reasons: less GVHD and quicker availability.

For example, if a patient has acute leukemia, has received chemotherapy, and is currently in remission, it may be realized that this remission is unlikely to last. As a consolidation, one may propose a transplant. If the patient does not have a donor in the family, there is intrinsic delay in the search of a matching bone marrow donor because one is dealing with a volunteer; the average time between the initiation of the procurement and a transplant is anywhere from 3–4 months. Some patients may not be able to afford a 4-month wait. In this case, a cord blood transplant may provide faster access to hematopoietic (blood) stem cells.

H&O Is there a possibility that cord blood may contain preleukemic content?

MD Yes this is a remote possibility, as we cannot be certain that a newborn cord blood donor will not develop leukemia sometime later in his/her lifetime. To limit this possibility, we take a comprehensive medical history and do not collect cord blood from any mother or father who has had leukemia or other cancers themselves or in any of their first degree relatives. There have been very few reports of cord blood donors developing leukemia after the donation. This has been reported to the cord blood banks, and those units were immediately removed from the inventory.

Additionally, cord blood units are subjected to the same screening as a bone marrow or peripheral blood stem cell transplant (eg, cell dose, mother and baby screened for infectious diseases, HIV, hepatitis, etc.). If the cord contains a low cell dose (typically less than a total of 1 billion cells), it is not acceptable for clinical use. Around 20–50% of units that are procured are usually accepted into the inventory.

H&O What are the key points to achieve a successful transplant?

MD A high cell dose is one of the major determinants of a successful cord blood transplant. It minimizes complications and expedites the establishment of the new blood and immune system in the recipient.

Most experts will agree that a cell dose of 2×10^7 total nucleated cell per kilogram of patient weight is an acceptable dose for a transplant. The vast majority of inventories will not have units that would achieve this cell dose for a 70-kg person; there are simply not enough cells that can be collected from a single unit. Although we are improving our collection techniques, which include milking the placenta to procure every cell possible, dose limitation remains a major problem for larger patients.

Because of this limitation, my colleagues and I have tried several strategies: 1) combining 2 units of cord blood to obtain more cells and 2) cultivating cord blood cells *ex vivo*. To cultivate, we put the cord blood cells in liquid culture with growth factors and other nurturing elements and let them expand for 14 days in a bag in the incubator (ie, an oven).

Under the leadership of Dr. Elizabeth Shpall, we conducted a clinical trial where we randomized 71 patients with advanced leukemias or lymphomas to receive either of the following 2 treatments: a standard cord blood transplant where unmanipulated blood stem cells from 2 umbilical cords are given or the experimental treatment

where the patient receives unmanipulated cells from 1 umbilical cord plus cells from a second umbilical cord where the CD34-positive “stem” cells responsible for engraftment were isolated and expanded in the laboratory. The premise of the study was to give as many cells to the recipient as possible, trying to correct some of the earlier problems we encountered with delayed production of neutrophils and platelets.

The question of whether 2 units are better than 1 unit was also controversial (as the choice for the control group), but our bias was that 2 units was the best control. In the expanded arm, as a precaution, we did not manipulate both of the 2 units given, in case the unit that we worked on did not function or was somehow affected by the growth factors used in the liquid culture system.

What we concluded with our preliminary analysis is that this approach is safe. However, we did not see statistically significant improvements in the speed of recovery.¹ One problem that we faced with our expansion technique was the substantial loss of critical cells with the CD34 cell isolation procedure and the lack of reproducibility. For some cord blood, we observed excellent expansions, and in others, the cells did not grow as well. This inconsistency may be due to a number of variables—the techniques of collection, expansion, etc. But we have since altered our techniques and are now culturing the entire cord blood unit in conjunction with bone marrow mesenchymal stem cells, seeing much more consistent results in terms of expansion.

H&O How may this expansion technique change treatment?

MD This technique needs to be studied further. However, slowly and surely we are making improvements in time to engraftment and the engraftment failure rate with our latest cord blood expansion strategy. The success for cord blood transplants has been documented for smaller adults and children, but there is still a major need for patients who are not only minorities, but also those who have a low cell dose. Ultimately, a randomized trial comparing the best expansion strategy versus unexpanded cord blood will be required to confirm superiority; the only randomized trial that we have conducted over the past 5 years employed our old expansion method as described above. Although the results between the 2 arms were not significantly different, there was a trend toward improved engraftment, which stimulated continued interest in the improved expansion technologies. We will be submitting another abstract to the American Society of Hematology annual meeting this year, in which we will be discussing significantly better expansion and faster engraftment.

H&O What research advancement do you expect to see with cord blood transplants?

MD I think that large trials will be conducted in order to define which patients are more likely to benefit from cord blood transplantation. We should not overstate the impact of expansion techniques as they are currently expensive and labor intensive. However, they are being refined continually, and reductions in hospital stay due to expansion techniques will more than offset the costs of cord blood expansion procedures in the future. Two institutions—our laboratory at M.D. Anderson Cancer Center and Dr. Colleen Delaney's group at the Seattle Cancer Care Alliance—are currently working on cord expansion improvements with rapid engraftment in the patients to date.

In terms of a more long-term view, cord blood can also be seen as a strong source of hematopoietic stem cells—the only type of stem cells in our body that can be produced in large amounts—used for regenerative medicine. Therefore, there is great interest in seeing cord blood cells as a source of stem cells that has the potential to become other organs (eg, pancreas, liver), not just blood.

References

1. De Lima M, McMannis JD, Saliba R, et al. Double cord blood transplantation (CBT) with and without ex-vivo expansion (EXP): a randomized, controlled study. *Blood (ASH Annual Meeting Abstracts)*. 2008;112: Abstract 154.