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Should double cord blood transplants be the preferred choice when a sibling donor is unavailable?

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Abstract

Umbilical cord blood transplant is an important alternative stem cell source for both children and adults with hematologic malignancies. Umbilical cord blood units are rapidly available and have less stringent human leukocyte antigen (HLA) matching requirements. Mismatch at two antigens actually improves the risk of relapse for umbilical cord blood transplant recipients with relatively low risk of severe acute or chronic graft vs host disease. However, umbilical cord blood transplant is associated with an inferior neutrophil recovery rate when compared to other stem cell sources. It is for this reason that we have explored 'double unit umbilical cord blood transplants,' not only as a platform for evaluating the safety and effectiveness of new methods of ex vivo expansion or methods of enhanced homing, but also as an approach itself to remedy the problem of limited cell dose, particularly for adults.

Keywords

umbilical cord blood transplant; double; single; mismatch; HLA; graft vs leukemia

Introduction

Umbilical cord blood transplantation is a relatively new transplant option with an estimated 15,000 cord blood transplants having been performed to date. With interest in double cord blood transplants growing, it is important to consider whether double cord blood transplant is a preferred choice when a sibling donor is not available. To determine this, physicians must first ask what we are looking to achieve in patients with acute leukemia, and whether the alternatives to allogeneic transplant are achieving the desired goal. Allogeneic transplantation is an attractive option for a specific subpopulation of patients due to the graft vs leukemia effect observed in allogeneic hematopoietic stem cell recipients. However, allogeneic transplantation is not without risks, either from the direct effects of the cytoreductive therapy itself or the slow immunological reconstitution. It is undeniably clear that even in recipients of human leukocyte antigen (HLA)-matched bone marrow or HLA-matched peripheral blood from an unrelated donor, patients still face high risks of transplant-related complications and mortality. With every HLA mismatch at the allele level, the risk of death is increased by approximately 10%.

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Despite the existence of over 10 million bone marrow donors worldwide, many patients still cannot find a match. Donor availability varies by ethnicity. While Caucasians identify a matched donor around 50% of the time, Hispanics have a 35% chance of finding a donor, and only 20% of African Americans find a donor.

The goals of transplant for acute leukemia patients are clear. We need a treatment plan that is associated with low transplant-related complications, minimal period of neutropenia, absence of acute and chronic graft vs host disease, and rapid immune recovery while maintaining a potent graft vs leukemia effect. In addition, suitable donors must be made available to all patients regardless of ethnic and racial background. Optimally, the transplantation procedure should be technically easy so that it can be administered most anywhere. Requirements for sophisticated graft manipulations or pharmacological agents that are not readily available would be limiting. Further, the graft must work in the nonmyeloablative setting to benefit the large subset of the patient population who are not fit for the fully ablative approach.

Umbilical cord blood

The fetal immune system has unique properties that are advantageous in regard to transplantation. Fetal T cells proliferate normally in the presence of alloantigens but do not kill target cells in vitro in the same way as allogeneic T cells from an adult donor. The fetal immune system also contains highly immunosuppressive cells, like T-regulatory cells and circulating trophoblasts that secrete high levels of interleukin-10. These cells probably play an important role in maternal-fetal tolerance and prevent rejection of the mother from the baby's cells and vice versa. At the outset of cord blood transplantation, it was hoped that these characteristics might lead to less HLA restriction and, therefore, wider application, as well as to reduce the incidence of graft vs host disease.

In contrast to peripheral blood or bone marrow from an unrelated donor where HLA-typing is performed at the allele level at HLA A, B, C, and DR (Table 1), cord blood is typed at the antigen level for HLA A and B, and allele level for HLA DR with HLA C not considered. It is for this reason, and the fact that matching is most commonly required for 4 of the 6 antigens, that most patients are able to identify a suitably matched cord blood donor despite the relative paucity of banked units worldwide (approximately 350,000).

To determine how mismatched umbilical cord blood compares to the 'gold standard' of HLA-allele-matched bone marrow, a retrospective analysis was performed first in pediatric patients with acute leukemia.¹ All patients were under the age of 16 and had either acute lymphocytic leukemia or acute myeloid leukemia. Comparing outcomes between the different stem cell transplant sources, we evaluated engraftment, risks of acute and chronic graft vs host disease, transplant-related mortality and relapse, and probability of overall survival. Those patients who received a transplant from a matched bone marrow donor had a higher risk of grade 2–4 acute graft vs host disease than those who received an umbilical cord blood transplant regardless of matching. Umbilical cord blood transplants were also associated with almost half the risk of chronic graft vs host disease risk. While transplant-related mortality increased with each degree of HLA mismatch, risk of relapse was reduced. Therefore, overall survival and event-free survival was similar for mismatched cord blood transplants and matched and unmatched bone marrow transplants, while matched cord blood transplants appeared to have a slightly higher overall probability of survival. While the improvement with matched cord blood was statistically significant, the study included only a small number of patients.

The Cord Blood Transplantation Study was a prospective phase II study to determine the maximum acceptable level of HLA disparity for single umbilical cord blood transplants.² The study included pediatric patients with hematologic malignancies, but a majority of patients had acute myeloid leukemia or acute lymphoblastic leukemia in first or second remission. The

study also retrospectively assessed the impact of allele level HLA typing at HLA A, B, C, DR, and DQ, which was a novel aspect of this particular analysis. Patients who received umbilical cord blood from a donor matched at 9 of 10 or 10 of 10 alleles showed an exceptionally high survival rate. However, even patients who received umbilical cord blood with 5–8 mismatches demonstrated good survival that overlapped with survival in patients transplanted with cord blood mismatched at 2–5 mismatches. While the maximum level of HLA mismatch that can be tolerated remains unclear, most centers have adopted a limit of 2 mismatches using antigen level A and B typing.

To determine how mismatched umbilical cord blood compares to the ‘gold standard’ of HLA-allele-matched bone marrow and peripheral blood in adults, a second retrospective analysis was performed again in patients with acute leukemia. In this analysis, in contrast to the study with children, adult patients receiving matched bone marrow and matched peripheral blood transplants demonstrated a trend towards higher overall survival than recipients of umbilical cord blood, but the findings were not statistically significant.³ Clearly, the analysis demonstrated a major barrier for the successful use of umbilical cord blood in adults due to the poor rate of neutrophil recovery after umbilical cord blood transplant. Substantial efforts are underway to address this significant limitation.

Double umbilical cord blood transplants

The poor neutrophil recovery rate after transplant prompted exploration of ex vivo expansion or the utility of mixing two umbilical cord blood units partially HLA-matched with each other. At the University of Minnesota, each umbilical cord blood unit must have a minimum cryopreserved nucleated cell count of 1.5×10^7 and ≤ 2 HLA mismatches with each other and ≤ 2 HLA mismatches with the recipient. The selection of one versus two umbilical cord blood units is based principally on cell dose but in the context of the degree of HLA mismatch. If a single umbilical cord blood unit has a cell dose $> 3.0 \times 10^7/\text{kg}$, only one unit is needed, but if the cell dose is lower, two umbilical cord blood units are combined to reach the minimum cell dose (Figure 1). Only 25%–30% of the patient population is eligible for a single umbilical cord blood unit transplant, with nearly all other patients able to identify an adequate double umbilical cord blood graft.

At the University of Minnesota, the cumulative incidence of neutrophil recovery and engraftment is 93% at a median of 21 days after double unit umbilical cord blood transplant, which appeared to be better than engraftment rates previously observed with a single umbilical cord blood transplant at lower cell doses. While these data were not generated as part of a randomized trial, they did suggest that double unit umbilical cord blood transplants were safe and may be a suitable stem cell source for adult patients who cannot otherwise find a suitable adult donor. While three-quarters of patients received a graft with 2 mismatched antigens, transplant-related mortality was 22% at 6 months, and leukemia-free survival was 63%, with an 18% probability or incidence of relapse. This study marked the first time that results in adults who received double unit umbilical cord blood transplants appeared to be superior to outcomes typically reported for children who nearly always receive a single unit umbilical cord graft. The low relapse rate prompted further investigation.

Nonmyeloablative regimens

At the University of Minnesota,^{4,5} a nonmyeloablative regimen of 50 mg/kg cyclophosphamide, 200 mg/m² fludarabine, and 200 cGy of single fraction total body irradiation has been used for older patients or those who have existing comorbidities. The patients receive either a large single unit (dose > 3.0) or double unit umbilical cord blood graft depending on cell dose. Patients who receive this regimen experience a rapid wave of recovery. As with other nonmyeloablative regimens, the initial wave of hematopoietic recovery is host-

derived, ultimately being donor-derived after the first month after the transplant. Almost all (94%) of the patients achieve engraftment at a median of 12 days. As with recipients of a full cytoreductive regimen, dual chimerism is common, particularly at early time points, with one unit ultimately winning out. Still, no factor has been identified that permits a prediction as to which of the two units will ultimately give rise to hematopoiesis long term.

Importantly, older patients who receive this nonmyeloablative regimen experience low transplant-related mortality (19%), and an overall survival rate of 45% for patients with both lymphoid and myeloid malignancies. Risk factors for mortality include the presence of comorbidities or grade 3–4 acute graft vs host disease. Together these data suggest that allogeneic transplantation may be a reasonable option for some patients regardless of age.

Graft vs leukemia effect and immune recovery

Because umbilical cord blood transplant may be associated with less graft vs host disease, there has been a general concern that the graft vs leukemia effect may also be diminished. Information on the graft vs leukemia effect and immune recovery in recipients of double umbilical cord blood transplant is beginning to emerge. Patients with acute myeloid leukemia or acute lymphocytic leukemia in first or second remission who received a double umbilical cord blood transplant appear to have a lower risk of relapse as compared to those transplanted with a single unit. Multivariate analysis shows that double vs single unit transplant is the only factor other than disease stage at time of transplant to be predictive of relapse risk. The predictive value of the number of umbilical cord blood units also holds true for lymphoid malignancies.⁷

These results suggest that the graft vs leukemia effect may be enhanced in recipients of two units, though the reason for this is still unclear. Nearly all double unit recipients received units with two mismatched antigens, which may create an in vivo mixed leukocyte reaction. While only a hypothesis, it is possible that this enhanced alloreactivity may result in reduced risk of relapse.

Alternatively, reduced risk of relapse might be driven by the degree of HLA mismatch. Data from the Eurocord registry showed that patients who received a single umbilical cord blood unit with 2 antigen mismatches had a lower risk of relapse than patients who received an HLA-matched umbilical cord blood unit. A study from the Center for International Blood and Marrow Transplant Research showed that the risk of relapse was lower in recipients of 4 of 6 matched recipients as compared to recipients of HLA matched marrow. Greater patient numbers are required to compare results in recipients of matched versus mismatched umbilical cord blood.¹ The same effects may hold true in double umbilical cord blood transplant, but this remains to be proven.

Immune recovery is just now beginning to be assessed. Based on absolute lymphocyte counts over time, there is no difference in immune recovery for patients with acute leukemia who received either a large single umbilical cord blood transplant or a double unit transplant. However, for patients with acute myeloid leukemia, preliminary analysis suggests that the rapidity of absolute lymphocyte recovery and use of double unit umbilical cord blood transplant may be significantly related to better overall treatment-related mortality and survival. Those patients who received a double unit transplant had better outcomes than those who received a single unit, and patients who had a very rapid absolutely lymphocyte count recovery had better outcomes than those with delayed recovery.

An ongoing randomized trial comparing single vs double unit umbilical cord blood transplants in children and adolescents with high-risk leukemia and myelodysplasia should be able to

distinguish whether there is an improved antileukemic effect and improved immune recovery for those receiving two units.⁸

Conclusion

It is too early to definitively say that double umbilical cord blood transplant should be the preferred stem cell choice when a sibling donor is unavailable. However, it is clear that the co-infusion of two umbilical cord blood units extends the application of transplant in general to nearly all patients. Furthermore, umbilical cord blood is rapidly available, it now has a high rate of engraftment with improved cytoreductive therapies and higher thresholds for cell dose, and it is generally associated with a low risk of grade 3 or 4 acute graft vs host disease and extensive chronic graft vs host disease. Double unit umbilical cord blood transplant may also serve as a platform for evaluating the safety and efficacy of new graft manipulations that may further improve upon the time to neutrophil recovery and engraftment.

While there are obstacles to overcome, such as speeding the pace of neutrophil recovery and making donor lymphocyte infusion available for those with donor lymphocyte-responsive disease, this modality is likely to increase in popularity. If for no other reason, umbilical cord blood permits us to find a donor rapidly without risk of attrition—particularly important for patients with acute leukemia.

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Figure 1. When to use one vs two umbilical cord blood units
Abbreviations: UCB, umbilical cord blood.

Table 1

Definitions of HLA match in 2009

HLA	Unrelated BM/PBSC	Unrelated UCBT
A	Allele level	Antigen level
B	Allele level	Antigen level
C	Allele level	Not considered
DR	Allele level	Allele level
DQ	Not considered	Not considered

Abbreviations: BM, bone marrow; HLA, human leukocyte antigen; PBSC, peripheral blood stem cell; UCBT, umbilical cord blood transplant