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Cord blood versus haploidentical stem cell transplantation for hematological malignancies

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ABSTRACT

Umbilical cord blood (UCB) and haploidentical donor stem cell sources represent common alternative donor strategies used when a matched sibling donor (MRD) or matched unrelated donor (MUD) is not available for hematopoietic stem cell transplantation (HSCT). Both donor sources require less stringent human leukocyte antigen (HLA) matching and thereby increase the donor pool for patients without a complete HLA-matched donor. Although a randomized trial comparing these donor sources is ongoing, currently available comparisons rely on observational data and small phase II trials. In hematologic malignancies, both donor sources offer the chance of eradicating disease, albeit with different results for engraftment time, graft failure, graft-versus-host disease (GVHD), transplant-related mortality (TRM), and relapse risk. This review focuses on comparing those outcomes and providing clinicians with evidence to help guide the decision between these alternative donor sources.

1. Introduction

When considering hematopoietic stem cell transplantation (HSCT) for a patient with a hematologic malignancy, the standard approach involves searching for a human leukocyte antigen (HLA)-matched related donor (MRD) or a matched unrelated donor (MUD). Only about 30% of patients will have a matched sibling donor [1]. As ethnic diversity increases, it is imperative to have a strategy to identify an alternative stem cell source when an adult MUD cannot be identified. The currently available approaches include a partially HLA-mismatched unrelated donor (MMURD), a haploidentical related donor, and an umbilical cord blood (UCB) stem cell product.

A haploidentical donor refers to a complete half HLA mismatch (generally 3/6 or 4/8) from a related donor. Haploidentical HSCT is performed in a variety of ways. One approach dubbed the Perugia regimen from Italy consists of conditioning with total-body irradiation, thiotepa, fludarabine, and anti-thymocyte globulin (ATG) with a high dose of $CD34^{+}$-selected stem cells [2]. Another regimen originally implemented by the John Hopkins group uses post-transplant cyclophosphamide to reduce the risk of graft-versus-host disease (GVHD) [3]. The regimen from China consists of high-intensity conditioning involving cytarabine with granulocyte colony-stimulating factor (G-CSF)–primed bone marrow (BM) and peripheral blood stem cells (PBSC) and ATG as part of GVHD prophylaxis [4]. Although it is usually easy to find and collect a related haploidentical donor, the major disadvantage of haploidentical donors is the HLA disparity. UCB stem cell products are cryopreserved and stored so they are available very quickly [5]. The minimal number of T cells in an UCB product allows it to be used across HLA barriers. Typically UCB stem cell products are HLA-mismatched at 1–6 antigens or alleles. The disadvantage is the small size of the product, which limits the stem cell dose in adults and often requires the use of a second UCB product.

Comparative observational studies have examined the differences between haploidentical or UCB stem cell sources and MRD/MUD transplants. These studies are difficult to interpret as patients who proceed to an alternative donor HSCT generally will have a high risk of disease recurrence warranting the increased risk that comes with an alternative donor stem cell source. Furthermore, the lack of prospective trials makes the heterogeneity among patients and physician preference difficult to control. Until such studies as the Blood and Marrow Transplantation Clinical Trials Network randomized comparison of UCB and haploidentical transplantation (BMT-CTN 1101, NCT01597778) are complete, physicians are left to cautiously interpret the existing data in making these important decisions. This review will explore the patient-related, disease-related, and transplant protocol-related factors that together uniquely affect the clinical outcomes of an individual patient.

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2. Engraftment time

When comparable conditioning regimens and cellular products are used, cell dose, engraftment time and reliability with MRD, MUD, and haploidentical donors are similar. This translates into a neutrophil engraftment time of 15–20 days for a BM haploidentical transplant [6,7] and 10–15 days for a PBSC haploidentical transplant [8,9].

In a study of more than 1,000 patients who received a single UCB stem cell product, the median total nucleated cell (TNC) dose prior to cryopreservation was 5.2×10^7/kg (range, 1.1–34.8) [10]. This is a smaller amount collected than with haploidentical donors, and after losses from cryopreservation and thawing, the median TNC dose infused from a single UCB product is approximately 2 to 4×10^7/kg [11,12]. Two UCB products are often used in an effort to increase the effective stem cell dose; this increases the TNC and $CD34^+$ cell dose infused and reduces the duration of cytopenias in adults, but still results in a median neutrophil recovery of at least 20-25 days, slower than anticipated with haploidentical transplant recipients [13–15]. It is reasonable to anticipate at least a 7-day prolongation in time to neutrophil recovery in adults receiving a double UCB transplant (21.5 days *v* 13 days) and a delay in platelet recovery from a median of 19 days in MUD to 41 days in UCB recipients [16]. Research to expand stem cells in UCB units has demonstrated improvements in neutrophil and platelet recovery times and may ameliorate this important barrier to UCB transplantation [17].

3. Graft failure

Graft failure can reflect insufficient or damaged stem cells in the donor product or can be due to the immune response from the recipient against the donor cells. Immunologically mediated rejection can be caused by sensitization of the recipient to non-shared HLA antigens. In UCB transplantation, there are few passively transferred T cells from the donor to protect against graft rejection and this may be more problematic than in haploidentical transplant because of the lower TNC and $CD34^+$ cell doses infused.

Graft failure with haploidentical transplantation remains a concern when compared to matched donors due to the HLA incompatibility. A recent analysis by the Center for Blood and Marrow Transplantation (CIBMTR) reported that neutrophil and platelet engraftment rates were similar for haploidentical HSCT with unmanipulated BM and post-transplant cyclophosphamide compared with MUD transplants [18]. The only exception to this was in the myeloablative conditioning (MAC) setting where the rate of neutrophil recovery with haploidentical transplant was lower than with MUD transplant (90% *v* 97%, respectively, $P = .02$). The Perugia regimen, which uses a high $CD34^+$ cell dose (13.8×10^6/kg), resulted in a primary engraftment failure rate of 9%, but this was reversible with the infusion of $CD34^+$ cells from the same or a different donor [2]. In patients receiving the Hopkins strategy of post-transplant cyclophosphamide with a T-cell–replete BM graft, the graft failure rate was 1% in MAC [19] and 12%–13% in reduced-intensity conditioning (RIC) haploidentical transplant [3,20]. Huang et al used a combination of T-cell–replete BM and G-CSF–primed PBSC with an augmented MAC regimen that included ATG, which resulted in almost no primary engraftment failures [21]. If graft rejection does occur after haploidentical transplantation, it is difficult to re-transplant patients who have become sensitized to unshared alleles or antigens.

With UCB transplantation, graft failure rates are generally higher than with haploidentical transplantation. With RIC UCB transplant, the rate of graft failure is close to 10% [15,22–24]. Ruggeri et al, in a large analysis of more than 1,000 single-unit UCB MAC transplants, found that 12% experienced graft failure by day 60. The likelihood of engraftment beyond day 30 declined rapidly with a residual probability of engraftment after day 42 of only 5% [10]. Rocha et al also reported a high graft failure rate of 20% with MAC single UCB transplant [12].

With the use of two UCB units, engraftment failure rates are improved but still not comparable to haploidentical transplant. In a European study comparing UCB and haploidentical transplant with a variety of conditioning regimens and GVHD prophylaxis strategies, the rate of neutrophil engraftment was significantly lower with UCB than haploidentical transplant (91% *v* 84%) [25]. In parallel phase II trials of RIC double UCB and RIC haploidentical transplantation with post-transplant cyclophosphamide, primary graft failure rates were 10% and 2%, respectively [23]. If engraftment failure follows UCB transplant, there is no opportunity to return to the donor for more stem cells. Thus, either additional UCB needs to be used and the recipient must survive the additional period of cytopenias, or a haploidentical donor transplant may be attempted. Salvage RIC haploidentical transplantation has been used with some success after graft failure from UCB transplantation [26].

4. Graft-versus-host disease

The balance between graft failure and GVHD is difficult in haploidentical donor HSCT. Strategies to improve either complication of HSCT with haploidentical donors include using high doses of stem cells, in vivo or ex vivo T-cell depletion, or post-transplant cyclophosphamide. None of these strategies have been compared directly with each other, and the risk of graft failure needs to be weighed against GVHD in each of these strategies. In haploidentical HSCT studies that employ high-intensity conditioning, graft failure rates have been low, but acute GVHD has been 40%–60%, despite the use of ATG [21,27,28]. In regimens that use a high dose of $CD34^+$ stem cells with a standard MAC regimen plus ATG for GVHD prophylaxis, the rates of acute and chronic GVHD are low (8% and 3%, respectively), but with higher graft failure rates [2]. Both approaches continue to have drawbacks: slow post-transplant immune reconstitution in patients who receive T-cell–depleted transplants and GVHD in those who receive T-cell–replete grafts [29]. The approach pioneered by Johns Hopkins using post-transplant cyclophosphamide to prevent GVHD has proven to be very effective requiring no stem cell manipulation. The rates of acute grade II–IV, acute grade III/IV, and chronic GVHD with this strategy have been reported to be 16%, 7%, and 30%, respectively, with MAC and 19%, 2%, and 34%, respectively, with RIC [18].

The less stringent HLA matching needed when selecting an UCB unit for transplantation is not associated with an increased risk of GVHD-related mortality. In 205 patients over the age of 50 with acute myeloid leukemia (AML) in first remission undergoing UCB transplantation, the rate of acute grade II–IV GVHD was 35%, comparable to MUD transplant, but chronic GVHD was 28%, significantly lower than MUD transplantation [30]. One study showed that UCB and haploidentical transplants were associated with slightly lower rates of acute and chronic GVHD when compared with matched sibling and unrelated donor transplantation [31]. In parallel phase II trials of UCB or haploidentical transplantation using post-transplantation cyclophosphamide conducted by the BMT-CTN, the grade II–IV GVHD rate was 40% for UCB transplant recipients and 32% for haploidentical transplant recipients. The grade III/IV acute GVHD rates were 21% and 0% for UCB and haploidentical transplants, respectively. Chronic GVHD was also higher in UCB transplants; 25% compared with 13% in haploidentical transplant at 1 year [23]. In the European