Review Article

Allogeneic Haematopoietic Stem Cell Transplantation without a Matched Sibling Donor: Current Options and Future Potential

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Abstract

Introduction: Allogeneic haematopoietic stem cell transplantation (HSCT) has been used to treat a variety of malignant and non-malignant diseases. For patients who do not have a matched sibling donor or a optimally matched unrelated donor (MUD) for transplantation, other graft sources have been used, including mismatched haploidentical related donors and umbilical cord blood (CB). Materials and Methods: A literature review and comparison of HSCT with MUD, haploidentical donors and CB donors was performed. The relative value of MUD and CB donor recruitment was calculated based on search-hit ratios of respective registries. Results: The choice of haematopoietic stem cell (HSC) source for transplantation remains difficult, and is dependent on disease stage, the centre's experience, HLA-matching and cell dose. It remains a lengthy procedure to identify and procure HSC from an acceptably matched unrelated donor, which may lead to disease progression in some patients. In these cases, alternatives such as haploidentical transplants or CB transplants can offer a chance for timely treatment. Although results of haploidentical transplant have improved in some centres, this approach is less successful in many other centres embarking on this transplant technique. However, there is the prospect of availability of HSC donors for almost every patient if the challenges of haploidentical HSCT can be overcome. CB transplantation has been established as a valid alternative for patients who cannot identify a suitably matched unrelated donor quickly enough. Some centres even prefer CB as a HSC source to unrelated donor bone marrow (BM) for paediatric patients. Conclusion: Further increases in the size and diversity of CB inventories may realise the potential of every patient having access to at least a 5/6 matched CB unit of adequate cell dose (70-fold relative value for each CB unit banked versus each BM donor recruited). Prospective comparisons of MUD, CB, and haploidentical HSCT are needed to validate the optimal HSC source for transplant in specific diseases.

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Introduction

Allogeneic haematopoietic stem cell transplantation (HSCT) has been used to treat a variety of malignant and non-malignant diseases, particularly of the blood and immune system (e.g. leukaemia, haemoglobinopathies and primary immune deficiencies).[1] Best results with allogeneic HSCT are seen in patients receiving a graft from a human leukocyte antigen (HLA) matched sibling. However, as no more than 30% of patients will have an HLA-identical sibling, much effort has been devoted to the establishment of bone marrow (BM) registries for HSCT. Various registries of volunteer donors worldwide have grown to include over 11 million potential volunteers, increasing the probability of finding a donor matched at HLA-A, B, C, and DRB1 to 60% to 70% for most Caucasian patients. However, HLA haplotypes vary in frequency among different ethnic groups, and patients of ethnic minorities or mixed ancestries still have a low probability (~10%) of identifying a match in registries dominated by Caucasian donors.[2]

For patients without a matched sibling or unrelated donor, other graft sources have been used; these include mismatched haploidentical related donors and umbilical cord blood (CB). These alternative sources significantly expand the donor pool and are more rapidly available than matched unrelated donor (MUD) grafts. Almost all patients have a haploidentical parent, child, sibling or relative who can serve almost immediately as a donor.[3] CB is a

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cryopreserved haematopoietic stem cell (HSC) source that can be procured readily, and which requires less stringent HLA matching because mismatched CB transplants cause less severe graft-versus-host disease (GVHD) than unrelated donor peripheral blood or BM transplants.[4] While both these stem cell sources could circumvent the difficulties faced in finding MUD donors, haploidentical transplants are complicated by graft rejection, GVHD, and delayed immune reconstitution, while the low cell dose of a single CB unit and the longer engraftment time after CB transplants remain barriers to therapeutic success.

In this review, we summarise the results of recent studies evaluating the use of matched unrelated donors, haploidentical donors and CB for transplantation in patients with acute leukaemia, and discuss the advantages, limitations and current research associated with each HSC source. Because improved outcomes with unrelated CB transplants have led to recommendations that CB can be a good alternative source for adults and a preferred source for children with acute leukaemia, we performed an analysis on the value of banking CB versus BM in this paper, from which we have made certain recommendations for the future growth of HSC registries.

Matched-unrelated Donor Transplants

Optimal unrelated donor-recipient matching requires a minimum of 8/8 HLA alleles (A, B, C, DRB1)[5] and a single mismatch at any of these loci is associated with significantly worse survival, treatment-related mortality (TRM), and more frequent acute GVHD. The role of mismatches at DQB1 and DPB1 on clinical outcomes[6,7] is presently still uncertain. Although early experience with MUD transplants showed inferior outcomes to matched sibling transplants, advances in HLA-typing techniques allowing better matching of donor to recipient have improved the prognosis.[8] A recent prospective study investigating outcomes after transplant with 10/10 allelic (HLA-A, B, C, DRB1, DQB1) MUD or HLA-identical sibling grafts for patients with standard risk haematological malignancies (74% acute leukaemia) found that overall survival, disease-free survival (DFS), TRM, relapse and acute GVHD were not dependent on donor type.[9]

Disease-specific series have also been published. An analysis of adults with high-risk or very high-risk acute lymphoblastic leukaemia (ALL) undergoing HSCT from matched sibling or unrelated donors found similar 5-year DFS for patients transplanted in the first complete remission (42% for sibling and 45% for MUD) but not in the second complete remission (40% vs 17%; $P = 0.1$).[10] However, Russell et al[11] reported that the use of a myeloablative conditioning regimen incorporating busulfan, fludarabine and 400 cGy total-body irradiation gave equivalent 2-year DFS for patients receiving related or unrelated donor grafts in the first or second complete remission (77% and 71%, respectively). In paediatric patients with ALL receiving sibling or unrelated transplant, no difference in 5-year DFS (39% and 54% respectively) and TRM (19% and 11%, respectively) was reported.[12] A study in children younger than 18 months with acute leukaemia also found similar 3-year DFS in recipients of related BM, unrelated BM or CB grafts.[13]

For HSCT in patients with acute myelogenous leukaemia (AML), a retrospective analysis found no significant difference in 5-year DFS between related and unrelated donor transplantation in both good-risk (40% and 62%, respectively) and poor-risk patients (25% and 21%, respectively).[14] Reduced-intensity transplantation (RIT) has been investigated as an approach to extend the benefits of allogeneic HSCT to patients who are older or who have significant co-morbidities. A study of RIT in high-risk elderly patients (median age, 60 years) with secondary AML or myelodysplastic syndrome found that the 2-year overall survival did not differ between related and unrelated donors (25% and 39% respectively).[15]

Because of improved results with well-matched unrelated donor transplants, many experts have suggested that recommendations for matched sibling transplants could possibly be extrapolated for 8/8 allele (A, B, C and DRB1) or 10/10 allele (A, B, C, DRB1 and DQB1) matched MUD transplants in future. However, these requirements also mean greater difficulty in finding a donor. Furthermore, another disadvantage that remains is the delay in identifying a matched donor. Currently, patients can identify a donor suitable for transplant only after a median waiting time of 3-5 months, provided one can be found, during which disease progression and relapse may occur.[16] The delay is due to the need to contact the donor, perform high resolution HLA typing, recall the donor for health screening and infectious disease testing and then to schedule a date for BM harvesting or stem cell harvesting at a time suitable for the donor. Many donors also default or change their minds during this process, resulting in further delays and a need to start this process all over again. Further studies are required to determine how clinical outcome worsens with mismatches at specific HLA loci, to help guide decisions of whether to proceed with transplant from an identified partially matched unrelated donor, or to continue with donor search.

Haploidentical Related Donor Transplant

Where a matched donor is not available, an alternative that has been explored is the use of fully haploidentical donors with 3 of 6 HLA antigen mismatches (A, B and DRB1). These mismatched transplants may require positive

selection of $CD34^+$ cells in peripheral blood stem cell (PBSC) grafts, which can attain a high $CD34^+$ cell recovery rate with effective T cell depletion (> 4.5 log). Megadoses of these purified $CD34^+$ cells can then overcome the barrier of residual anti-donor cytotoxic T-lymphocyte precursors (CTL-*p*) after highly immuno- and myelo-ablative conditioning regimens, allowing full donor-type engraftment in over 95% of adult patients.[17] The inclusion of ATG and other T-cell antibodies (OKT3) in some protocols allows T cells to be depleted in vivo, further reducing the incidence of GVHD.[18] Non-myeloablative preparative regimens with a combination of in vivo and ex vivo T-cell depletion have also allowed engraftment of partially matched stem cells, leading to survival rates that are comparable to myeloablative transplants.[19]

The best survival rates with haploidentical transplants have been reported by the Perugia institute, at 55% and 28% for adults with AML and ALL transplanted in remission, which compares favourably with MUD HSCT.[20] However, poor results are obtained when patients are transplanted with advanced disease, because profound T-cell depletion to allow engraftment of the mismatched graft also limits the graft-versus-leukaemia (GVL) effect needed to control leukaemia. A recent series of 266 adult patients with acute leukaemia confirmed poor outcomes when haploidentical transplants were performed on patients with active disease: 2-year DFS was a dismal 0% and 7% for AML and ALL, respectively.[21] An analysis of 118 children with ALL who underwent myeloablative HSCT using grafts with ≥2 out of 6 HLA disparities also found that DFS is largely dependent on disease stage: 3-year DFS was 32%, 28% and 0% for patients transplanted in CR1, CR2 or CR3, and advanced disease, respectively. Notably, patients in remission undergoing transplants at less experienced centres had significantly lower DFS than at experienced centres (17% vs 49%, $P = 0.002$), with results at experienced centres comparing favourably with paediatric studies using unmanipulated MUD grafts.[22]

Although rejection and GVHD issues with crossing a major histocompatibility barrier have been resolved with high CD34+ cell doses and extensively T-cell depleted grafts, delayed immune reconstitution leading to significantly high infection-related mortality rates remains a major problem. Strategies are being developed to improve immune reconstitution after transplant. This includes the use of cytokines such as IL-7 and keratinocyte-growth factor to enhance thymopoiesis,[23,24] as well as graft manipulation to deplete alloreactive T cells while preserving regulatory T cells and T cells specific for tumour-associated or viral antigens.[25] Negative selection of T cells rather than positive selection of $CD34^+$ cells can also retain natural killer (NK) cells, monocytes, and dendritic cells important for immune reconstitution and GVL effect.[26] No lethal infections have been observed in a group of 35 children with high-risk or refractory haematological malignancies transplanted with CD3/19 depleted haploidentical peripheral blood stem cells using non-myeloablative conditioning.[27]

Cord Blood Transplants

Cord blood transplants (CBT) lead to lower severity of GVHD compared to bone marrow transplants (BMT) for any degree of HLA match, allowing transplants with up to 2 HLA antigen mismatches between donor and recipient.[4] Despite the decrease in GVHD, GVL effect is maintained, and relapse rates remain comparable to transplantation with unrelated BMT.[28] Both the cell dose and HLA match level of the CB graft have been shown to affect engraftment and survival, and a 4 to 6 out of 6 matched CB unit with a cell dose of at least 2.5-3 x 10^7 TNC/kg is generally considered acceptable for a single-unit transplant currently.[29] It has been proposed that a higher cell dose may be able to overcome the adverse impact of mismatching in the setting of 4/6 matched CBT in paediatric patients,[30] and further studies are needed to determine the interaction between HLA-matching and cell dose to guide selection of the most optimal CB unit for transplant.[31,32]

Outcomes of CBT in children with acute leukaemia have been extensively reported with outstanding results.[33] Comparisons of unrelated CBT and BMT in paediatric patients found delayed engraftment, higher early TRM, but similar survival rates despite a higher number of HLA mismatches in the CB grafts.[34] A meta-analysis comparing outcomes of unrelated CBT and BMT in 161 paediatric patients found a lower incidence of chronic GVHD with CBT but no differences in the incidence of grade III-IV acute GVHD and 2 year overall survival.[35] This was despite the fact that most CBT recipients had 1-2 antigen mismatched grafts while almost all the BM donors had fully matched donors. Recently, Eapen et al[30] reported that the 5-year DFS was similar after transplantation with either 1-2 antigen mismatched CB or 8/8 matched BM, and DFS was possibly higher after transplant of 6/6 matched CB compared to 8/8 matched BM (60% vs 38%, $P = 0.0406$).

Two registry studies and a retrospective study have been conducted to compare outcomes of CBT and unrelated BMT in adults. CBT consistently led to significantly slower haematopoietic recovery and higher graft failure, but while the United States (US) study found significantly lower survival after CBT compared to BMT,[36] the European study reported no difference in survival and the Japanese study reported higher survival with CBT.[37,38] Differences in the time period of transplants, HLA compatibility and cell dose of the CB graft, as well as time to donor search

may explain the different conclusions in these studies. Hwang et al[35] compared outcomes after unrelated CBT and BMT in 966 adult patients, and found no difference in TRM and DFS, suggesting that 1-2 antigen-mismatched CB can be considered as a reasonable alternative to 6/6 BM for adults. Two partially HLA-matched CB units have been transplanted in adults to overcome cell dose limitations, and studies generally reported an improved rate of haematopoietic engraftment without increased incidences of severe acute GVHD.[29]

The less stringent HLA-matching requirement of CB transplants is a clear benefit that improves patient access to HSCT, especially racial and ethnic minority patients who have a smaller pool of registered marrow donors. Analysis of the probability of identifying an optimal match in a given registry size found that while a 6/6 matched marrow cannot be identified for patients with rare alleles even if the registry size is infinite,[39] a 300,000 cord unit inventory may be sufficient to allow every paediatric patient, and up to 96% of adult patients, the ability to identify a CB unit that is 4-6/6 matched with a volume of at least 2.5 x 10^7 TNC/kg.[40] Furthermore, better minority representation can potentially be achieved in some CB banks, due to the directed collection in hospitals with a diverse maternal population and the perception of CB donation as low-risk in comparison to BM donation.[41] In Singapore, for example, 15% of the population is ethnic Malay and less than 2% are registered BM donors. However, donation from Malay mothers for CB banking has been very forthcoming, at 22.8%.

New strategies to improve haematopoietic recovery after CBT are being studied, including double CBT,[29] ex vivo expansion of CB progenitor cells,[42,43] direct injection of CB cells to the BM,[44,45] co-infusion of mesenchymal stem cells or partially matched peripheral blood $CD34^+$ cells.[46,47] To reduce the relapse rate after CBT, antigen-specific T cells and NK cells have been generated from naïve CB-derived T cells for post-transplantation adoptive immunotherapy.[48,49] CBT is also effective after non-myeloablative preparative regimens, which extends the treatment to elderly patients or patients with significant comorbidities with no matched sibling donor.[50]

Cord Blood Banking

Given the promising results obtained with CBT, many agencies support the establishment and expansion of public CB banks to increase the likelihood of transplant candidates matching to a CB unit. We performed an analysis to estimate the registry size needed to allow similar probabilities of a patient finding a 6/6 matched BM or 5/6 matched CB, using data provided by the National Marrow Donor Programme in a 32,108-sized registry. The 5/6 match probability for a CB in a registry size of 32,108 is approximately 91.3%, which is close to the chance of finding a 6/6 match in a sample of 2,267,518 BM donors (87.3%). This gives a 70-fold relative value for each CB unit banked versus each BM donor recruited, assuming that the matched CB unit will have sufficient cells to meet the needs of the patient. Adjusting the data to take into account the probability of the cord unit meeting the requirements of 40 kg individuals based on inventory data from the Singapore Cord Blood Bank, we found that the relative value of CB banking and BM recruitment is estimated to be approximately 16:1.

As a cord inventory that is many times smaller than a BM registry can allow similar match probabilities, we strongly advocate that new emerging economies seeking to divest governmental or charitable funds into establishing large BM donor registries could be better served by at least investing a good proportion into building good quality public CB banks. Furthermore, unlike BM donors who may become unavailable due to failure of health screening, loss to follow-up or subsequent refusal, a banked CB unit is already qualified, tested for infectious disease and readily available for transplant. A new CB bank in Mexico experienced a high uptake rate (10 of its 201 stored cord units) in the first 2 years of operation, suggesting that public CB banks can greatly enhance a developing country's efforts to establish an unrelated donor transplantation programnme.[51] Continued efforts to prioritise the collection of CB from racial and ethnic minorities can further improve the cost-effectiveness of CB banking.

Conclusions

The choice of HSC source for transplantation in patients with acute leukaemia and other haematological diseases remains difficult, and is dependent on disease stage, the centre's experience, and HLA-matching and cell dose of the HSC source. It remains a lengthy procedure to identify and procure HSC from an acceptably matched unrelated donor, which may lead to disease progression or relapse in some patients. In these cases, alternatives such as haploidentical transplants or CB transplants can offer a chance for timely treatment. Although the results of haploidentical transplant have improved in some centres, this approach is not useful in the setting of advanced disease and continues to be plagued by high infection-related deaths and poor long-term survival in many centres embarking on this transplant technique. However, there is a very large upside of the immediate availability of HSC donors for almost every patient if the challenges of haploidentical HSCT can be overcome. CB transplantation has been established as a valid alternative for patients who cannot identify a suitably matched unrelated donor quickly enough. Some centres even prefer CB as a HSC source to unrelated donor BM for paediatric patients. Further increases

in the size and diversity of CB inventories may realise the potential of every patient having access to at least a 5/6 matched CB unit of adequate cell dose. Prospective comparisons of MUD, CB, and haploidentical HSCT are needed to validate the optimal HSC source for transplant in specific diseases.

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