SCIENTIFIC PAPER

Unrelated donor haematopoietic stem cell transplantation for adult patients with haematological malignancies

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Unrelated donor (URD) is an acceptable source of stem cell grafts for adults. With the growth in available URD, improved human leukocyte antigen (HLA) typing technology and better understanding of HLA matching, the number of URD haematopoietic stem cell transplantation (URD-HSCT) is increasing dramatically in recent years. Peripheral blood stem cells have surpassed bone marrow as the preferred stem cell source for URD-HSCT, and more unrelated cord blood transplantations have been successfully performed in adults. Majority of URD transplants are for haematological malignancies, and acute leukaemia has become the most common disease, while the percentage of older patients receiving URD transplants is increasing. Clinical advances in URD-HSCT have greatly improved the outcomes, which are now comparable to related donor HSCT, however, transplant-related mortality (TRM) remains the most considerable problem in URD-HSCT. It is worth noting that non-myeloablative or reduced-intensity conditioning regimens have been introduced and utilised increasingly in URD-HSCT recently, which reduce the TRM and expand eligible patients for URD-HSCT. Since the family size is decreasing in China, URD represents the most common alternative source of stem cell for HSCT. However, further improvements are necessary in the setting of URD-HSCT.

Introduction

Allogeneic haematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for most haematological malignancies. More and more alternative donors, such as unrelated donor (URD) and cord blood (CB), have been used for patients who need a transplant without an human leukocyte antigen (HLA) compatible donor in the family, and the increase of URD-HSCT was higher than the general increase in allogeneic HSCT during the same period.[1-3] The growth of donor registries worldwide greatly facilitates the transplant activity, and the volunteer donor pool has expanded to nearly 12 million adult donors. Refinements in HLA typing and matching, advances in transplant procedures and supportive care might favourably influence the transplant outcomes. The disease-free survival (DFS) and overall survival (OS) of URD-HSCT have improved by nearly 10% in past years,[3] which are now comparable to related-donor HSCT. Nowadays, more than 2000 stem cell transplants per year have been performed in more than 50 bone marrow (BM) transplant units in mainland China.[4] Since the family size is decreasing in China, URD represents the most common alternative source of stem cell for allogeneic HSCT.

Key words
Donor selection; Hematopoietic stem cell transplantation; Hematologic neoplasms; Transplantation conditioning

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Donor registries worldwide

There are a number of national and international donor registries, and the coordination and cooperation have facilitated the transplant activity worldwide. Bone Marrow Donors Worldwide (BMDW) is the continuing effort to collect the HLA phenotypes of volunteer stem cell donors and CB units, including 59 stem cell donor registries from 43 countries and 41 CB banks from 25 countries, and the current number of donors and CB units has reached 12 million. National Marrow Donor Program (NMDP) in the United States is one of the largest international donor registries, and over 4300 patients received URD-HSCT through NMDP every year.[5] Racial and ethnic diversities, however, remain the major challenges to the donor registries. The main suppliers of unrelated haematopoietic stem cells in Mainland China are Chinese Marrow Donor Program (CMDP) and Tzu Chi Stem Cell Center. Tzu Chi Stem Cell Center is the earliest donor registry for Chinese population, and it has more than 320 000 donors now. The CMDP was initiated in 1992 and restarted service for the public in 2001. By the end of 2008, CMDP has grown to include almost 938 000 donors, and it is expected to reach 1 million by 2009, and has facilitated over 1100 URD donations. The processing of HLA data systems has made significant enhancements for more efficient and accurate URD and CB unit searches, and the median time to identify

a suitable URD is now about 2 months. At the same time, the international HSCT societies carry out activities to improve the outcomes of HSCT.

Human leukocyte antigen typing and matching: finding the best donor

Human leukocyte antigen matching plays an important role in engraftment, incidence and severity of graft-versus-host disease (GVHD) and survival. As serologic typing and cellular assay are known to have many limitations, advances in molecular HLA typing and matching technology have facilitated more rapid identification of better HLA-matched donors. Lee et al[6] evaluated the outcomes of URD-HSCT from 1988 to 2003 (n=3857) through NMDP and showed that a single mismatch allele, at HLA-A, -B, -C, or -DRB1 was associated with a higher mortality and a 9 to 10% absolute decrease in survival. In multiple studies, mismatches at HLA-B and/or -C seemed to be better tolerated than mismatches at HLA-A and -DRB1, and single mismatches at DQ seem not to influence mortality, but with adverse effect combination with other mismatches.[6,7] The impact of HLA-DPB1 matching in URD-HSCT is still not well-defined. Several studies showed mismatching for HLA-DPB1 in URD-HSCT was associated with an increased risk for acute GVHD, but may protect against relapse.[8,9] Donor-recipient matching for HLA-A, -B, -C, -DRB1 and -DQB1 has been the standard matching comprise in URD-HSCT. For those patients who have no family donor, an HLA-matched URD is available for 30 to 70% of cases.[10] A single antigen or allele HLA mismatch is acceptable, particularly when balanced against the risk of the disease progression, but the permissive mismatches should be accepted by transplant physicians for HSCT.[6,11]

Further studies are needed to evaluate and refine the permissive and non-permissive mismatching strategies, which allow wider latitude in mismatched donor selection.[8] Beyond HLA typing, genetic variants encoding minor histocompatibility antigens, immune response genes and pharmacogenes are being studied to determine whether additional genetic matches or mismatches may cause additional transplant risks.[10,12,13]

Source of stem cells

There are great changes of stem cells source in the past years. Since 1989, peripheral blood stem cells (PBSC) mobilised by granulocyte colony-stimulating factor (G-CSF) have been increasingly used for related and URD-HSCT. According to the reports recently, PBSC grafts have surpassed BM as the preferred stem cell source and comprise the majority of adult URD-HSCT.[2,4,5] The URD-HSCT of PBSC leads to a faster leukocyte recovery in comparison to BM.[14,15] Transplantation of PBSC was, however, always associated with higher acute GVHD and chronic GVHD than transplantation of BM, but there were no differences seen in transplant-related mortality (TRM), relapse, DFS, or OS.[16,17] Unlike PBSC in related donor transplanted for advanced leukaemia,[15] there was no overall advantage in survival for one graft type over another in patients with advanced leukaemia in URD-HSCT.[16] Furthermore, Garderet et al[18] observed that patients with acute lymphoblastic leukaemia (ALL) allografted with a matched URD may have a lower survival with a PBSC compared to BM. These data suggest that the source of transplant cells needs to be evaluated by disease when dealing with URD-HSCT. It is necessary to better define the role of PBSC grafts, and a phase-III randomised multicentre trial comparing G-CSF mobilised PBSC with BM transplantation from HLA-matched URD is under way.

Cord blood as an alternative source of stem cells has the clear benefits of rapid availability and a reduced stringency of requirement for HLA match. The number of CB transplantations (CBT) for adults being performed is increasing dramatically. Most recent studies demonstrated that unrelated CBT after myeloablative conditioning could be safely and effectively used for adults with haematological malignancies and non-malignant disorders.[1,19] The outcome of single-unit CBT in adults with 4-6/6 HLA-A, -B and -DRB1 matched has been compared with BM/PBSC transplantation from HLA-matched or HLA-mismatched URD.[20,21] Cell dose remains the major limitation of CBT, and it is exciting that some studies demonstrated better HLA match can largely compensate for low cell dose.[1,22] Eurocord has suggested the cell dose is dependent upon the

無關供者異基因造血幹細胞移植治療成人惡性血液病的進展

無關供者異基因造血幹細胞移植（URD-HSCT）已成為異基因造血幹細胞移植的一種主要方式。在過去的二十年間，HLA高分辨基因學配型技術及遺傳免疫學的進展有效地指導了適合供者的選擇，全球供者庫和巨大協作網絡的建立更是為尋求適合的供者提供了便利，URD-HSCT的數量有了飛速的增長。在URD-HSCT中，外週血幹細胞已取代骨髓成為無關供者捐贈的主要方式；而臍帶血幹細胞因其獲得方便且患者可耐受相對較高程度的HLA配型的不一致，在成人無關供者造血幹細胞移植中的應用也日益增多，並取得了較好的療效。盡管移植相關死亡仍是影響URD-HSCT療效的首要原因，但隨著近年來URD-HSCT技術方案的成熟和支持治療的進步，移植現狀已獲得明顯的改善，多項臨床研究顯示URD-HSCT達到了與同胞供者移植接近的療效。非清髓預處理方案在URD-HSCT中的應用日益增多，其顯著降低了移植相關死亡的發生，隨之越來越多的老年及有合並症的患者有機會獲得移植治療。隨著我國獨自子女家庭的增多，URD-HSCT必將成為一種主要的造血幹細胞移植方式，針對不同的病人選擇最佳的供者及移植方案以提高移植的療效是移植醫生要考慮的主要問題。

HLA match, which is HLA match 6/6 >3, 5/6 >4, and 4/6 >5×10^7/kg, respectively.[22] Now, double-unit CB grafts and non-myeloablative conditioning regimen have been used to improve the outcome of unrelated CBT in adults.[1,23]

Unrelated donor haematopoietic stem cell transplantation for haematological malignancies

Over the past decades, URD-HSCT has been performed for a wider variety of diseases with steady improvement in transplant outcome. The majority of transplants are for haematological malignancies. The percentage of older patients receiving URD-HSCT is increasing dramatically, and over 10% adult transplant recipients are over the age of 60 years.[3]

Acute myeloid leukaemia (AML) is the most common indication for URD-HSCT. In the latest report of NMDP, and patients with AML accounted for 39% of URD-HSCT followed by myelodysplastic syndrome (MDS) [14%], non-Hodgkin's lymphoma (NHL) [14%] and ALL [13%].[3] In China, AML, ALL and MDS are the most common diseases for URD-HSCT. It was reported that OS of AML, MDS and ALL following myeloablative URD-HSCT was 30-70%, 32-70% and 40-70%, respectively.[3,24-27] The URD-HSCT for NHL and multiple myeloma (MM) has two separate categories—a primary URD transplant or a URD second transplant with a prior autologous transplant, and most of the latter patients had non-myeloablative conditioning. The OS of NHL and MM was about 37-68% and 40-66%, respectively.[3,28-31] There has been a marked trend to do fewer transplants for chronic myeloid leukaemia, which only accounted for 10% recently, due to the introduction of tyrosine kinase inhibitors such as imatinib.[2,3] However, allogeneic HSCT is often appropriate for second-line therapy for patients who develop resistance to imatinib, and the current OS is about 50%.[3] Disease stage has the most important impact on the outcome of URD-HSCT. Multiple studies and our data suggest that for patients with leukaemia in first complete remission (especially those with high-risk features and lacking related donors) URD-HSCT should be considered.[27,32,33]

Transplant-related mortality is high in URD-HSCT, and the important risk factors for TRM are degree of HLA matching, disease status at transplant, patient and donor age, as well as performance status. The most recent report of NMDP showed that TRM had declined significantly over the years. For leukaemia and MDS patients, 2-year TRM declined to 32%, and for NHL and Hodgkin disease to 37%.[3] GVHD remains a lethal complication after URD-HSCT. The incidence of grade II-IV acute GVHD ranged from 10 to 80%, and severe (grade III-IV) acute GVHD is responsible for 15 to 40% of mortality.[34] Corticosteroids are still used as first-line therapy, and tumour necrosis factor antibodies (infliximab or etanercept) are effective for steroid refractory acute GVHD.[35,36] Furthermore, cellular therapy of GVHD, such as mesenchymal stem cells (MSCs), might be effective for patients with severe acute GVHD. A recent study showed a high response of 70.9% to steroid-resistant acute GVHD following the treatment with MSCs.[37] In addition, graft-versus-leukaemia (GVL) effect is more potent using URD compared with related donors, with a lower incidence of relapse in URD-HSCT. It is important for physicians to consider the balance between efficacy and risk of TRM of URD-HSCT.

Non-myeloablative conditioning regimen for unrelated donor haematopoietic stem cell transplantation

Despite the improvements in transplant procedures, URD-HSCT is still associated with higher TRM due to toxicity of conditioning regimen, severe GVHD and infectious complications. Non-relapse mortality (NRM) rates of over 50% are commonly reported in patients over 40 years. Non-myeloablative or reduced-intensity conditioning (RIC) regimens have been introduced in URD-HSCT since the late 1990s, and conditioning-related toxicity is realistically less than conventional conditioning. A lower incidence of GVHD after URD transplants with non-myeloablative conditioning compared with myeloablative conditioning was initially expected. However, some studies demonstrated grade II-IV acute GVHD in approximately 39 to 74% of patients and grade III-IV acute GVHD in 8 to 22% of patients,[38-40] and the incidence of chronic GVHD was 41 to 67%.[38,39] Compared with the transplantation of related donors with non-myeloablative conditioning, the use of URD had similar risks of developing grade III-IV acute GVHD and did not increase either NRM or overall mortality.[39,40]

Non-myeloablative conditioning regimens have become common in URD-HSCT performed recently. The most dramatic growth in URD-HSCT is mainly due to the use of non-myeloablative transplants, which have greatly expanded transplant therapy to older patients. Giralt et al[38] reported the first 285 received RIC URD transplants by NMDP, and patients of which were older (55 vs 33 years) and had more advanced disease than recipients of myeloablative transplants during the same period.[38] The 5-year survival was 23%, and the NRM was about 38%.[38] Prognostic factors for better OS were earlier disease stage, longer time to transplant from diagnosis, better HLA match, better performance status, and use of PBSC. However, patients receiving URD-HSCT with non-myeloablative conditioning always have poor-risk disease and advanced age.[31,38,40] The URD-HSCT with non-myeloablative conditioning appears

to be promising. However, it should continue to be explored in clinical trials.

Conclusion

With the growth in available URD and CB units which enable more patients to access HSCT therapies, clinical advances in URD-HSCT have led to expanded patient eligibility and improved outcomes. Recently, URD-HSCT is increasingly being used as treatment for haematological malignancies. However, physicians continue to face challenges in terms of the selection strategies for the best suitable donor, the appropriate transplant timing and procedures for different diseases, and ultimately improve the outcomes.

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