Strategies in Haploidentical Stem Cell Transplantation in Adults

Erişkinlerde Haploidentik Kök Hücre Naklinde Stratejiler

Ulaş D. Bayraktar1,2, Stefan O. Ciurea1

1Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
2Mercy Cancer Center, Medical Oncology, Hematology, Ardmore, OK, USA

Abstract:

Haploidentical related donors are alternative stem cell sources for patients without human leukocyte antigen (HLA)-matched related or unrelated donors. Immediate access to the donor, availability for patients with rare haplotypes, ease of stem cell procurement, and lack of a requirement for a physical cord blood bank or an extensive HLA database render this type of hematopoietic stem cell transplantation particularly attractive despite the high histoincompatibility barrier between the recipient and the haploidentical graft. In this review, we answer the following questions: 1) What are the current transplant strategies used to overcome the histoincompatibility barrier in haploidentical stem cell transplantation and their clinical results? 2) How should we choose the donor when there is more than one available haploidentical donor? 3) How does transplantation from haploidentical donors compare to that from umbilical cord blood?

Key Words: Haploidentical stem cell transplantation, HLA, GVHD

Özet:

Tam “human leukocyte antigen” (HLA) uyumlu bağışığı bulunamayan hastalar için bir diğer seçeneğin yarı-eşlenik akraba bağışıklardan alınacak kök hücrelerdir. Bağışığı ve hasta arasında aşılması gerekken yüksek HLA uyumsuzluğu, yarı-eşlenik akraba bağışıklarından kan kök hücre nakli (yarı-eşlenik kan kök hücre nakli [YKHN]); bağışık, annede ulaşılamayabilirlik, ender gorülen haplotipler için uygulanamayabilirlik, kök hücrelerin elde edilmesinde kolaylık ve kord kanı bankası/doku bankasından bağmışlığı dolayısıyla cazip bir yöntemdir. Bu derledede şu soruları cevaplanacaktır: 1) YKHN’de HLA uyumsuzluk barierini aşmak için kullanılan stratejiler ve sonuçları nelerdir? 2) Birden fazla yarı-eşlenik akraba bağışıcısının olması durumunda bağışçı nasıl seçilmelidir? 3) YKHN’in korddan kök hücre nakline göre avantaj ve dezavantajları nelerdir?

Anahtar Sözcükler: Haploidentik kök hücre nakli, HLA, Graft Versus Host Hastalığı (GVHH)

Address for Correspondence: Ulaş D. BAYRAKTAR, M.D., Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
Phone: +1 (580) 223-7091
E-mail: darda.bayraktar@gmail.com

Received/Geliş tarihi: February 13, 2013
Accepted/Kabul tarihi: July 25, 2013
**Introduction**

Two-thirds of patients who require allogeneic hematopoietic stem cell transplantation (SCT) do not have a human leukocyte antigen (HLA)-matched related donor available [1]. A matched unrelated donor can be identified in only 50% to 60% of these cases. The chance of finding such a donor is particularly poor for patients whose ethnicity is under-represented in HLA databases. Haploidentical donors – parents, children, and half of siblings – are alternative stem cell sources for such patients without matched donors. The first successful SCT from a haploidentical donor (haploSCT) was reported in 1981 in a 10-month-old infant using an ex vivo T cell-depleted bone marrow graft from her father [2]. After 30 years of experience, transplanters are now better at overcoming the histoincompatibility barrier between the recipient and the haploidentical donor.

What are the current transplant strategies used to overcome the histoincompatibility barrier in haploSCT and their clinical results?

For successful haploSCT, both the patient's and the graft's immunity should be suppressed or modified to prevent graft failure and graft-versus-host disease (GVHD). Various strategies have been devised to achieve the required suppression without substantially increasing treatment-related mortality (TRM) arising from immunosuppression. These strategies may be studied in 2 groups: those utilizing ex vivo T cell-depleted grafts and those utilizing T cell-replete grafts.

With currently available magnetic selection methods, 3 to 5 logs of ex vivo T cell depletion (TCD) of the stem cell graft is possible [3], and this is the most effective method to prevent GVHD after SCT. Unfortunately, extensive TCD of the graft impairs engraftment and increases primary graft failure rates as more host immune cells survive post-SCT. In initial trials, T cell-depleted grafts from haploidentical donors were rejected in up to 50% of cases [4]. The risk of graft rejection may be reduced by intensification of the conditioning regimen [5,6], in vivo host TCD with antibodies [7], and increasing of the bone marrow (BM) inoculum (number of CD34+ cells infused) [8]. The most notable haploSCT protocol to date was devised at the University of Perugia in the 1990s, in which a “mega-dose” of CD34+ cells (while a threshold for the dose has not been defined, the reported minimum is 5.1x10^6 CD34+ cells/kg) derived from BM and peripheral blood after TCD was used with ablative conditioning and anti-thymocyte globulin [3,9]. While GVHD incidence was minimal and the graft rejection rate was acceptable, TRM due to infections remained an issue, which is the current focus of transplanters utilizing TCD grafts. Although ex vivo TCD in haploSCT is most commonly achieved by positive selection of CD34+ cells, negative selection of lymphocyte subsets through CD3/CD19 or TCRαβ retains other donor immune cells, i.e. natural killer (NK) cells, that may decrease the incidence of GVHD and exert a graft-versus-leukemia effect [10]. The strategies used in TCD haploSCT are summarized in Table 1 with their respective clinical results.

Without TCD of the graft, a higher-intensity GVHD prophylaxis regimen or selective inhibition of graft T cells becomes necessary to prevent GVHD after haploSCT. While Chinese researchers chose to intensify immunosuppression and prime the BM graft with granulocyte colony-stimulating factor (G-CSF) [11], researchers from Johns Hopkins led the way by selectively inhibiting graft immunity against donor cells using post-SCT cyclophosphamide [12,13]. One of the more established methods to be utilized in haploSCT, which was studied and reported in a recent Blood and Marrow Transplant Clinical Trials Network (BMT CTN) trial [14], post-SCT cyclophosphamide has little impact on stem cells and engraftment while primarily targeting donor lymphocytes activated by recipient antigens immediately after graft infusion. The rationale and clinical results of haploSCT strategies not utilizing TCD of the graft are summarized in Table 1.

Overall, while TCD results in lower GVHD incidence with acceptable engraftment rates when a “mega-dose” of CD34+ cells is used, a relatively high TRM rate primarily due to infections remains an issue. Furthermore, TCD requires an initial investment in facilities employing good manufacturing practice with cell selection instruments, i.e. CliniMACS, and expertise to run such facilities. The initial investment cost may be difficult to attain in developing and under-developed countries where haploSCT would be particularly valuable since residents of such countries are generally under-represented in international HLA databases. While haploSCT with T cell-replete grafts may lead to higher GVHD incidence, it allows the intensity of conditioning regimens to be reduced through host immunity suppression utilizing engraftment. However, the reduced intensity conditioning regimen used in most studies of post-SCT cyclophosphamide may lead to high relapse incidence in acute leukemic patients. At the MD Anderson Cancer Center, we compared the outcomes of haploSCT with TCD peripheral blood grafts to that with unmanipulated BM grafts after an identical ablative conditioning regimen (fludarabine-melphalan-thiotepa) [15]. Early results revealed significantly higher rates of overall and progression-free survival with unmanipulated BM grafts, primarily because of significantly lower TRM (16% vs. 42% at 1 year).

How should we choose the donor when there is more than one available haploidentical donor?

Most patients requiring SCT have more than one haploidentical donor. The presence of recipient antibodies against donor-specific HLA, killer immunoglobulin-like receptor (KIR) mismatch predicting NK cell alloreactivity, mismatch for non-inherited maternal vs. paternal alleles, degree of HLA mismatch between donor and recipient,
Table 1. Studies utilizing different strategies to overcome histoincompatibility barrier in hematopoietic stem cell transplantation from haploidentical donors.

| Reference       | Conditioning and GVHD prophylaxis | Rationale                                   | Patient characteristics | Engraftment and GVHD | Survival |
|-----------------|-----------------------------------|---------------------------------------------|-------------------------|-----------------------|----------|
| Aversa F, 2005 (3) | TBI 8 Gy day -8, Thio 5 mg/kg/day days -8, -7; ATG 5 mg/kg days -5 to -2, No post-SCT GVHD prophylaxis | Ablative conditioning for better disease control and to prevent graft rejection | n=104 Median age: 33 (9-64) | 94 pts (91%) engrafted Grade II-IV aGVHD in 8 pts (8%) cGVHD in 5 pts (7%) | TRM: 37% for pts in remission; 44% in pts with active disease 27 pts (26%) died of infections RI: 16% for pts in remission; 51% in pts with active disease EFS @ 3 yrs: 48% for pts in remission; 4% for pts with active disease |
| Amrolia PJ, 2006 (39) | Ablative: Cy 90 mg/kg, araC 12 g/m², TBI 1400 cGy, Almtz 12-40 mg RIC: TBI 450 cGy, Flu 120 mg/m², Almtz 40 mg Graft: Mega-dose CD34-selected PBSC Allo-depleted (through co-culture of donor T cells with recipient APCs followed by addition of immunotoxin against CD25 to eliminate activated T cells) infused on days 30, 60, 90 | Rigorous T cell depletion to prevent GVHD Alemtuzumab to prevent graft rejection Post-SCT infusion of T cells to hasten immune reconstitution – allo-depleted to prevent GVHD | n=61 Median age: 9 (2-58) | All engrafted Grade II-IV aGVHD in 2 pts (both after donor T cell infusion) cGVHD in 2 pts | 5 pts alive @ median follow-up of 33 mos |
| Federmann B, 2012 (26) | Flu 150 mg/m²; Thio 10 mg/m²; Mel 120 mg/m² OKT-3 3.5 mg/day days -5 to 14 Post-SCT MMF only if graft included ≥5x10⁶ CD3+ cells/kg Graft: CD3/CD19 depleted PBSC | RIC to decrease GVHD and TRM T cell depletion to prevent GVHD CD3/CD19 depletion used instead of CD34-selection to retain NK cells in graft OKT3 to prevent graft rejection – OKT3 preferred over ATG to spare NK cells | n=61 38 AML 8 ALL 6 NHL 4 MM 3 CML 1 MDS 1 CLL | All engrafted Grade II-IV aGVHD CI 46% cGVHD CI 18% | 3 primary graft failures NRM @ 2 yrs: 42% 18 pts (30%) died of infections RI @ 2 yrs: 31% EFS @ 2 yrs: 23% OS @ 2 yrs: 28% |
| Di Ianni M, 2011 (40) | TBI 8 Gy day -10, Thio 4 mg/kg days -10, -9, Flu 40 mg/m²/day days -10 to -6, Cy 35 mg/kg days -7, -6 Freshly isolated (by CD8 and CD19 depletion followed by CD25-selection) donor Tregs infused on day -4 Graft: Mega-dose of CD34-selected PBSC Varying doses of Tcons infused after graft infusion on day 0 | T cell depletion to prevent GVHD To hasten immune reconstitution post-SCT a fixed dose of Tcons infused with graft, which was preceded by Treg infusion to avoid GVHD Ablative conditioning to prevent graft rejection and for better disease control ATG was omitted to preserve infused Tregs and Tcons | n=28 High-risk heme malignancies | 26 pts (93%) engrafted Grade II-IV aGVHD in 2 pts No cGVHD | TRM 13 pts (50%) 8 pts (31%) died of infection 1 pt relapsed OS @ 1 yr: 46% |
| Grosso D, 2011 (41) | TBI 1.5 Gy BID days -9 to -6 2x10⁶ CD3+ cells/kg DLI day -6 Cy 60 mg/kg days -3 and -2 MMF and Tacrol after day -1 Graft: CD34-selected PB | 2-step transplantation to optimize donor T cell dose by: a) Infusing a fixed dose of donor T cells (DLI) followed by Cy to preferentially eliminate activated lymphocytes b) Infusing T cell-depleted PB graft after DLI to protect graft from Cy Ablative conditioning for better disease control and to prevent graft rejection | n=27 Median age: 52 (19-67) | No primary graft failures Grade II-IV aGVHD in 16 pts (60%) | RI: 30% OS @ 3 yrs: 48% |
| Study                          | Age Range | Disease Types                                                                 | Regimen                                                                 | Outcome Measures                  |
|-------------------------------|-----------|-------------------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------|
| Luznik, L, 2008 (13)          | 16-70     | AML, ALL                                                                       | Bu: Cy 1.8 g/m² days -2, -1; TBI 200 cGy day -1; Cy 14.5 mg/kg day -6, -5; | 2-year DFS: 51%                  |
|                               |           |                                                                                | Flu 30 mg/m² days 0-3; Flu 30 mg/m² days 0-3; Bu 3.2 mg/kg IV daily days 4-2; |                                  |
|                               |           |                                                                                | TBI 3.3 Gy days -8 to -6; Flu 30 mg/m² days -5 to -2; Cy 50 mg/kg on days 3 and 5; |                                  |
|                               |           |                                                                                | CsA 1 mg/m²/day 8 to 20; MMF 15 mg/kg 24h days 1 to 28; G-CSF-prime;       |                                  |
|                               |           |                                                                                | Unmanipulated BM                                                         |                                  |
| Lee KH, 2011 (42)             | 16-70     | AML, ALL, CML, MDS                                                             | Bu: Cy 1.8 g/m² days -2, -1; TBI 200 cGy day -1; Cy 14.5 mg/kg day -6, -5; | 2-year OS: 62%                   |
|                               |           |                                                                                | Flu 30 mg/m² days 0-3; Flu 30 mg/m² days 0-3; Bu 3.2 mg/kg IV daily days 4-2; |                                  |
|                               |           |                                                                                | TBI 3.3 Gy days -8 to -6; Flu 30 mg/m² days -5 to -2; Cy 50 mg/kg on days 3 and 5; |                                  |
|                               |           |                                                                                | CsA 1 mg/m²/day 8 to 20; MMF 15 mg/kg 24h days 1 to 28; G-CSF-prime;       |                                  |
|                               |           |                                                                                | Unmanipulated BM                                                         |                                  |
| Davies JK, 2008 (43)          | 18-70     | AML, ALL, CML, MDS                                                             | TBI 175 Gy BID days -6 to -3; Cy 1.8 g/m² days -2, -1; Short-course Mit; | 2-year OS: 55%                   |
|                               |           |                                                                                | CsA; Graft: ex vivo allogeneic induction with incubation of donor BM graft with recipient APCs and CTLA4-Ig |                                  |
|                               |           |                                                                                | Graft: Unmanipulated PB                                                  |                                  |
| Raiola AM, 2013 (44)          | 0.5-50    | AML, ALL, CML, MDS                                                             | Flu: 30 mg/m² days -6 to -2, 2, -2, Cy 14.5 mg/kg days -6, -5; TBI 200 cGy day -1; Cy 50 mg/kg days 3 and 5; Cy 1.8 g/m² day -2; | 2-year DFS: 55%                  |
|                               |           |                                                                                | Flu 30 mg/m² days 0-3; Flu 30 mg/m² days 0-3; Bu 3.2 mg/kg IV daily days 4-2; |                                  |
|                               |           |                                                                                | TBI 3.3 Gy days -8 to -6; Flu 30 mg/m² days -5 to -2; Cy 50 mg/kg on days 3 and 5; |                                  |
|                               |           |                                                                                | CsA 1 mg/m²/day 8 to 20; MMF 15 mg/kg 24h days 1 to 28; G-CSF-prime;       |                                  |
|                               |           |                                                                                | Unmanipulated BM                                                         |                                  |
| Brunstein CG, 2011 (14)       | 18-66     | AML, ALL, CML, MDS                                                             | Flu: 30 mg/m² days -6 to -2, 2, -2, Cy 14.5 mg/kg days -6, -5; TBI 200 cGy day -1; Cy 50 mg/kg days 3 and 5; Cy 1.8 g/m² day -2; | 2-year DFS: 51%                  |
|                               |           |                                                                                | Flu 30 mg/m² days 0-3; Flu 30 mg/m² days 0-3; Bu 3.2 mg/kg IV daily days 4-2; |                                  |
|                               |           |                                                                                | TBI 3.3 Gy days -8 to -6; Flu 30 mg/m² days -5 to -2; Cy 50 mg/kg on days 3 and 5; |                                  |
|                               |           |                                                                                | CsA 1 mg/m²/day 8 to 20; MMF 15 mg/kg 24h days 1 to 28; G-CSF-prime;       |                                  |
|                               |           |                                                                                | Unmanipulated BM                                                         |                                  |
| Huang XJ, 2009 (11)           | 2-56      | AML, ALL, CML, MDS                                                             | arac 4 mg/m² days -10,-9; Bu 12 mg/kg PO 6q6 days -8 to -6; Cy 1.8 g/m² days -5, -4; semustine 250 mg/m² day -3; rATG 2.5 mg/kg days -5 to -2; Graft: Combination of G-CSF–primed BM and PB | 2-year OS: 72%                   |
|                               |           |                                                                                | Graft: G-CSF–primed unmanipulated BM and PB                               |                                  |
| Di Bartolomeo P, 2013 (45)    | 18-70     | AML, ALL, CML, MDS                                                             | Various TBI- or non-TBI-based regimens: 64 ablative, 16 RIC, 16 RIC, 5 mg/kg days -4 to -1; CsA day -7 to day 180; | 2-year OS: 55%                   |
|                               |           |                                                                                | MDS, myelodysplastic syndrome, CMML chronic myeloid leukemia, MDS, myelodysplastic syndrome, BMF, bone marrow failure syndromes,                  |
|                               |           |                                                                                | NRM: non-relapse mortality, OS: overall survival, Treg: regulatory T lymphocytes, Tcom: conventional T lymphocytes, TDL: donor lymphocyte infusion, Tac6: Tac6, PB: peripheral blood, BM: bone marrow, AA: aplastic anemia, RBC: red blood cell, CMML chronic myelomonocytic leukemia, PNH: paroxysmal nocturnal hemoglobinuria, PFS: progression-free survival, LFS: leukemia-free survival, Bu: busulfan, Mtx: methotrexate, CsA: cyclosporin A, PD: progressive disease, MHC: major histocompatibility complex, TCR: T cell receptor, MF: myelofibrosis, MFD: myelodysplastic disorder. | 2-year OS: 55%                   |
v donor age, and ABO-match should be taken into account while deciding on the donor among available haploidentical candidates.

Transplant recipients may have developed anti-HLA antibodies against donor HLA antigens (donor-specific antibodies; DSAs) during pregnancy or after blood product transfusions. The presence of DSAs is associated with increased risk of primary graft failure after SCT [16,17,18,19]. Additionally, the level of DSAs in recipient serum is likely important. If a patient has DSAs against all haploidentical donors, selecting donors with the lowest antibody level may be appropriate. Treatment of recipients with plasma exchange or rituximab may also be reasonable and has been used in solid organ transplantations.

NK cells primarily attack hematopoietic cells, sparing solid organs [20]. In recipients lacking HLA class I alleles specific to the donor KIRs, donor NK cells may prevent GVHD and disease relapse by eliminating residual recipient antigen-presenting cells and leukemia cells [21,22]. Accordingly, KIR mismatch between recipient and donor has been associated with improved haploSCT outcomes [21,22,23]; however, this finding has been disputed by other researchers [24,25]. KIR mismatch may play a more pronounced role in SCT for myeloid malignancies [22,26]. Further studies are needed to verify the impact of NK alloreactivity and KIR mismatch on haploSCT outcomes.

Although a progressive increase in TRM with increasing genetic disparity has been historically reported, contemporary transplant strategies may negate this correlation by overcoming larger histoincompatibility barriers. In fact, Kasamon et al. reported no increased incidence of acute GVHD (aGVHD) and non-relapse mortality (NRM) after haploSCT from full-haplotype mismatched donors compared to those with better-matched donors [27]. Moreover, patients with more than 3 mismatches appeared to have better outcomes due to a lower relapse incidence.

Immunologic tolerance may develop between mother and fetus during pregnancy [28,29], leading to down-regulated immune responses if the mismatched haplotype between the recipient and the haploidentical donor is of maternal origin. Accordingly, patients with maternal donors were found to survive longer than those with paternal donors [30], and TRM was reported to be lower in patients with recipients mismatched for non-inherited maternal HLA compared to those with recipients mismatched for paternal antigens [31].

The immune system is subject to senescence with advancing age. Although no data exist on an association between donor age and outcomes after haploSCT, the findings of higher GVHD incidence and shorter survival after unrelated donor transplants from older donors compared to younger donors would probably apply for haploSCT, as well. Older multiparous women may be the least preferred donors for male recipients [32].

Studies have demonstrated that infusion of larger numbers of CD34+ cells improved outcomes after SCT [33,34,35]. Stem cell dose is also likely important in haploSCT, as can be inferred from the improved outcomes with megadoses of peripheral blood stem cells in TCD haploSCT [9]. Transplants involving a major ABO incompatibility require mononuclear cell separation to prevent a hemolytic reaction, which reduces the graft cell dose. If maximizing the infused stem cell dose is indeed important in haploSCT, then younger, larger donors without a major ABO incompatibility with the recipient should be preferred.

An in-depth review of donor selection in haploSCT is available from Ciurea and Champlin [32] and the proposed algorithm is shown in Figure 1.

How do transplants from haploidentical donors compare to those from umbilical cords?

For patients lacking an HLA-matched related or unrelated donor, umbilical cord blood (UCB) is another alternative stem cell source. UCB is more immune-plastic than

| Table 2. Comparison of hematopoietic stem cell transplantation from umbilical cord and haploidentical donors. |
|------------------------------------------|------------------------------------------|
| **Advantages**                           | **Umbilical cord**                        |
| - Short search and graft acquisition time| - Short search and graft acquisition time |
| - Availability for patients with rare haplotypes| - Availability for patients with rare haplotypes |
| - Easy rescheduling of infusion          | - Easy rescheduling of infusion          |
| - Does not require an umbilical cord bank or HLA database | - No potential for viral transmission |
| **Issues**                               | **Umbilical cord**                        |
| - Relatively high graft failure rates    | - Relatively high graft failure rates    |
| - Delayed immune reconstitution         | - Delayed immune reconstitution         |
| - Lack of T cell-mediated graft-versus-leukemia effect if ex vivo T cell-depleted grafts are used | - Delayed engraftment |
| - Ease of post-transplant cell acquisition for therapy, i.e. donor NK cell or lymphocyte infusion | - Potential for congenital disease transmission |
|                                         | - Inability to use post-transplant cellular therapy, i.e. donor lymphocyte infusion |
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Figure 1. Proposed algorithm for donor selection in haploidentical stem cell transplantation. DSA indicates donor-specific anti-HLA antibodies; MFI: median fluorescence intensity, NIMA: non-inherited maternal antigens, NK: natural killer. Reproduced from Ciurea and Champlin with permission (32).

Peripheral blood and bone marrow grafts; therefore, 2 or 3 out of 6 HLA mismatches are allowed for UCB transplants. However, use of UCB as a stem cell source has been limited until recently by the delayed engraftment and relatively high rate of primary graft failures due to the low volume and low CD34+ cell content. Use of double, instead of single, UCB has partially overcome these issues [36,37].

The advantages and disadvantages of haploSCT and UCB SCT are outlined in Table 2. Although they had not been systematically compared to each other, a recent parallel multi-center phase 2 trial by BMT CTN confirmed the utility of both double UCB and haploidentical donors as alternative stem cell sources [14]. Fifty patients in each arm, with advanced hematological malignancies, received either BM grafts from haploidentical donors or double UCB after similar conditioning regimens including fludarabine, cyclophosphamide, and low-dose total body irradiation (TBI). Grade II-IV acute GVHD and chronic GVHD incidences were numerically higher in the double UCB arm (40% vs. 32% and 25% vs. 13%), demonstrating efficacy of the post-SCT cyclophosphamide in the haploSCT arm. NRM at 1 year was 24% and 7% in the double UCB and haploSCT arms, while relapse incidence was 31% and 45%, respectively. One-year progression-free survival (PFS) was similar in both arms at 46% and 48%. Similarly, a retrospective analysis of the European Group for Blood and Marrow Transplantation (EBMT) database demonstrated significantly lower acute GVHD rates after haploSCT compared to UCB SCT between 1998 and 2002 [38]. A randomized BMT CTN study is ongoing in the United States, comparing SCT from haploidentical donors and UCB in patients with hematological malignancies.

With our current knowledge, it is difficult to recommend one stem cell source over another for patients without matched donors. Until a large-scale randomized prospective study shows one’s superiority, transplant centers will and should choose an alternative stem cell source based on their own expertise. However, T cell-replete haploSCT is clearly advantageous for countries and centers without the financial backing to invest in and maintain an umbilical cord bank. Despite these advantages and recent advances, haploSCT is a risky procedure with additional perils of late-onset chronic GVHD and infections due to the histoincompatibility barrier, late immune reconstitution, and intensified GVHD prophylaxis limiting its use to experienced centers.

Conflict of Interest Statement

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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