Review

DOI: 10.4274/Tjh.2013.0054

Strategies in Haploidentical Stem Cell Transplantation in Adults

Erişkinlerde Haploidentik Kök Hücre Naklinde Stratejiler

Ulaş D. Bayraktar[1,2], Stefan O. Ciurea[1]

[1]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[2]Mercy 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 bağışçı bulunamayan hastalar için bir diğer seçenek yarı-eşlenik akraba bağışçılardan alınacak kök hücrelerdir. Bağışçı ve hasta arasında aşılması gereken yüksek HLA uyumsuzluğuna ragmen, yarı-eşlenik akraba bağışçılarından kan kök hücre nakli (yarı-eşlenik kan kök hücre nakli [YKHN]); bağışçıya anında ulaşılabilirlik, ender gorülen haplotipler icin uygulanabilirlik, kök hücrelerin elde edilmesindeki kolaylık ve kord kanı bankası/doku bankasından bağımsızlığı dolayısıyla cazip bir yontemdir. Bu derlemede şu soruları cevaplandıracağız: 1) YKHN'de HLA uyumsuzluk bariyerini aşmak için kullanılan stratejiler ve sonuçları nelerdir? 2) Birden fazla yarı-eşlenik akraba bağışçısının 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
T cell-depleted grafts					
Aversa F, 2005 (3)	TBI 8 Gy day -8; Thio 5 mg/kg/day days -8, -7; rATG 5 mg/kg days -5 to -2 No post-SCT GVHD prophylaxis Graft: Mega-dose of CD34-selected PBSC	Ablative conditioning for better disease control and to prevent graft rejection Rigorous T cell depletion to prevent GVHD ATG to prevent graft rejection and GVHD Mega-doses of progenitor cells to improve engraftment	n=104 Median age: 33 (9-64) 67 AML (19 in CR1) 37 ALL (14 in CR1)	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/m^2, TBI 1400 cGy, Almtz 12-40 mg RIC: TBI 450 cGy, Flu 120 mg/m^2, Almtz 40 mg Graft: Mega-dose CD34-selected PBSC Allodepleted (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 – allodepleted to prevent GVHD	n=16 Median age: 9 (2-58) 7 AML (1 in CR1) 2 ALL 1 HL 1 CML 1 MDS 3 BMF	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/m^2; Thio 10 mg/m^2; Mel 120 mg/m^2 OKT-3 5 mg/day days -5 to 14 Post-SCT MMF only if graft included >5x10^4 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	3 primary graft failures Grade II-IV GVHD CI 46% cGVHD CI 18%	NRM @ 2 yrs: 42% 18 pts (30%) died of infections RI @ 2 yrs: 31% EFS @ 2 yrs: 25% OS @ 2 yrs: 28%
Di Ianni M, 2011 (40)	TBI 8 Gy day -10; Thio 4 mg/kg days -10, -9; Flu 40 mg/m^2/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 2x10^8 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) 17 AML (5 in CR1) 4 ALL 2 MDS 3 NHL (refractory) 1 AA	No primary graft failures Grade II-IV aGVHD in 16 pts (60%)	RI: 30% OS @ 3 yrs: 48%

T cell-replete grafts

Luznik L, 2008 (13)	Cy 14.5 mg/kg/day IV days -6, -5; Flu 30 mg/m^2 days -6 to -2; TBI 200 cGy day -1 Cy 50 mg/kg IV day 3 or days 3, 4; Tacrol from day 5 to 180; MMF day 5 to 35 Graft: RBC-depleted BM	RIC to decrease GVHD incidence Post-SCT Cy to prevent GVHD by selectively eliminating donor alloreactive T cells that are acutely activated after graft infusion by host antigens	n=68 Median age: 46 (1-71) 27 AML (12 in CR1) 4 ALL (2 in CR1) 1 MDS 6 CML/CMML 3 CLL 13 HL (refractory) 10 NHL (refractory) 3 MM (refractory) 1 PNH	Graft rejection in 9 pts (13%) Grade II-IV aGVHD 34% cGVHD CI 5% (2 doses of post-SCT Cy) and 25% (1 dose of post-SCT Cy)	NRM @ 1 yr: 15% EFS @ 2 yrs: 26% OS @ 2 yrs 36% EFS longer in lymphoid vs. myeloid malignancies (p=0.02)
Lee KH, 2011 (42)	Bu 3.2 mg/kg/day IV days -7, -6; Flu 30 mg/m^2 days -7 to -2 rATG 3 mg/kg days -4 to -1; CsA 1.5 mg/kg from day -1; Mtx 15 mg/m^2 on day 1 then 10 mg/m^2 days 3, 6, 11 Graft: Unmanipulated PB	RIC to decrease GVHD incidence ATG to prevent graft rejection and GVHD	n=83 Median age: 40 (16-70) 52 AML (12 in CR1) 16 ALL (3 in CR1) 15 MDS	No primary graft failures but early PD in 4 pts Grade II-IV aGVHD in 16 pts (20%) cGVHD CI 34%	TRM CI 18% RI: 27%-32% in pts with acute leukemia in CR; 79% in pts with refractory leukemia OS: 41%-60% in pts with leukemia in CR; 9% in pts with refractory leukemia
Davies JK, 2008 (43)	TBI 175 cGy BID days -6 to -3; Cy 1.8 g/m^2 days -2, -1 Short-course Mtx, CsA Graft: ex vivo alloanergy induction with incubation of donor BM graft with recipient APCs and CTLA4-Ig	Induction of allospecific anergy through blockage of CD80/86 on recipient APC. T cells require 2 signals for activation: MHC binding to TCR and co-stimulatory signal through CD28. Latter binds to CD80/86 on APCs	n=24 Age range: 0.5-50 21 high-risk heme malignancy (none in CR1, 14 with PD) 3 with bone marrow failure	2 (8%) graft failure Grade B-D aGVHD in 8 pts (38%) cGVHD CI 8%	TRM incidence 50% EFS and OS: 33% @ 10 yrs
Raiola AM, 2013 (44)	(A) Thio 5 mg/kg days -6 and -5; Flu 50 mg/m^2 days -4 to -2; Bu 3.2 mg/kg IV daily days -4 to -2 (B) TBI 3.3 Gy days -8 to -6; Flu 30 mg/m^2 days -5 to -2 Cy 50 mg/kg on days 3 and 5; CsA 1 mg/kg/day days 0 to 20; MMF 15 mg/kg q12h days 1 to 28 Graft: Unmanipulated BM	Post-SCT Cy to prevent GVHD by selectively eliminating donor alloreactive T cells that are acutely activated after graft infusion by host antigens Ablative conditioning to prevent graft rejection and for better disease control	n=50 Median age: 42 (18-66) 25 AML (9 in CR1) 12 ALL (2 in CR1) 5 lymphoma (chemorefractory) 4 MF (leukemic transformation) 4 MPD (blast crisis)	2 (4%) graft failures Grade II-IV aGVHD in 6 pts (12%) cGVHD CI 26%	6-month TRM: 18% RI: 22% (33% in pts with active disease at SCT) 18-month DFS: 51% 18-month OS: 62%
Brunstein CG, 2011 (14) BMT CTN 0603	Flu 30 mg/m^2 days -6 to -2; Cy 14.5 mg/kg days -6, -5; TBI 200 cGy day -1 Cy 50 mg/kg days 3, 4; Tacrol day 5 until 180; MMF day 5 until 35	RIC to decrease GVHD incidence Post-SCT Cy to prevent GVHD by selectively eliminating donor alloreactive T cells that are acutely activated after graft infusion by host antigens	n=50 Median age: 48 (7-70) 22 AML 9 ALL 12 NHL 7 HL	1 pt had primary graft failure Grade II-IV aGVHD CI 32% cGVHD CI 13%	NRM @ 1 yr: 7% RI @ 1 yr: 45% PFS @ 1 yr: 48% OS @ 1 yr: 62%
Huang XJ, 2009 (11)	araC 4 g/m^2 days -10, -9; Bu 12 mg/kg PO q6h days -8 to -6; Cy 1.8 g/m^2 days -5, -4; semustine 250 mg/m^2 day -3 rATG 2.5 mg/kg days -5 to -2; CsA day -9 onward; MMF 500 mg day -9 to 60; Mtx 15 mg/m^2 on day 1 then 15 mg/m^2 on days 3, 6, 11 Graft: G-CSF–primed unmanipulated BM and PB	Combination of G-CSF–primed BM and PB grafts may lead to faster engraftment without increased GVHD ATG to prevent graft rejection and GVHD Intensive GVHD prophylaxis Ablative conditioning to prevent graft rejection and for better leukemia control	n=250 Median age: 25 (2-56) 108 AML (67 in CR1) 142 ALL (82 in CR1)	249 (99%) engrafted Grade II-IV aGVHD in 115 pts (46%) Limited cGVHD in 61 (28%), extensive cGVHD in 31 (14%) pts	3-year TRM: 29% and 51% in high-risk AML and ALL 3-year RI: 20% and 49% in high-risk AML and ALL 3-year LFS: 55% and 25% in high-risk AML and ALL
Di Bartolomeo P, 2013 (45)	Various TBI- or non-TBI–based regimens: 64 ablative, 16 RIC ATG 5 mg/kg days -4 to -1; CsA day -7 to day 180; Mtx 15 mg/m^2 day 1 then 10 mg/m^2 days 3, 6, 11; MMF day 7 to 100; basiliximab 10-20 mg days 0 and 4 Graft: G-CSF–primed unmanipulated BM	Intensive GVHD prophylaxis G-CSF–primed BM graft to hasten engraftment without increasing GVHD PBSC were omitted to decrease GVHD incidence	n=80 Median age: 37 (5-71) 45 AML (21 in CR1) 15 ALL (8 in CR1) 5 HL 5 CML 3 MDS 2 NHL 2 MF 3 MM	1 pt had primary graft failure Grade II-IV aGVHD CI 24% cGVHD CI 17%	TRM CI @ 1 yr: 36% 11 pts (14%) died of infections RI @ 3 yrs: 26%-28% OS @ 3 yrs: 45% DFS @ 3 yrs: 38%

GVHD: Graft-versus-host disease, TBI: total body irradiation, Thio: thiotepa, rATG: rabbit anti-thymocyte globulin, SCT: hematopoietic stem cell transplantation, PBSC: peripheral blood stem cells, AML: acute myeloid leukemia, ALL: acute lymphoid leukemia, CR: complete remission, CR1: first CR, aGVHD: acute GVHD, cGVHD: chronic GVHD, TRM: transplant-related mortality, RI: relapse incidence, EFS: event-free survival, Cy: cyclophosphamide, araC: cytarabine, Almtz: alemtuzumab, RIC: reduced-intensity conditioning, Flu: fludarabine, APC: antigen-presenting cell, HL: Hodgkin lymphoma, CML: chronic myeloid leukemia, MDS: myelodysplastic syndrome, BMF: bone marrow failure syndromes, yr: year, mo: month, pt: patient, MMF: mycophenolate mofetil, NK: natural killer, NHL: non-Hodgkin lymphoma, CLL: chronic lymphocytic leukemia, MM: multiple myeloma, CI: cumulative incidence, NRM: non-relapse mortality, OS: overall survival, Treg: regulatory T lymphocytes, Tcon: conventional T lymphocytes, DLI: donor lymphocyte infusion, Tacrol: tacrolimus, 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: primary myelofibrosis, MPD: myeloproliferative disorder.

Table 2. Comparison of hematopoietic stem cell transplantation from umbilical cord and haploidentical donors.

	Haploidentical donor	Umbilical cord
Advantages	- Short search and graft acquisition time - Availability for patients with rare haplotypes - Easy rescheduling of infusion - Does not require an umbilical cord bank or HLA database	- Short search and graft acquisition time - Availability for patients with rare haplotypes - Easy rescheduling of infusion - No potential for viral transmission
Issues	- Relatively high graft failure rates - Delayed immune reconstitution - Lack of T cell-mediated graft-versus-leukemia effect if ex vivo T cell-depleted grafts are used - Ease of post-transplant cell acquisition for therapy, i.e. donor NK cell or lymphocyte infusion	- Relatively high graft failure rates - Delayed immune reconstitution - Delayed engraftment - Potential for congenital disease transmission - Inability to use post-transplant cellular therapy, i.e. donor lymphocyte infusion

vdonor 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 mega-doses 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

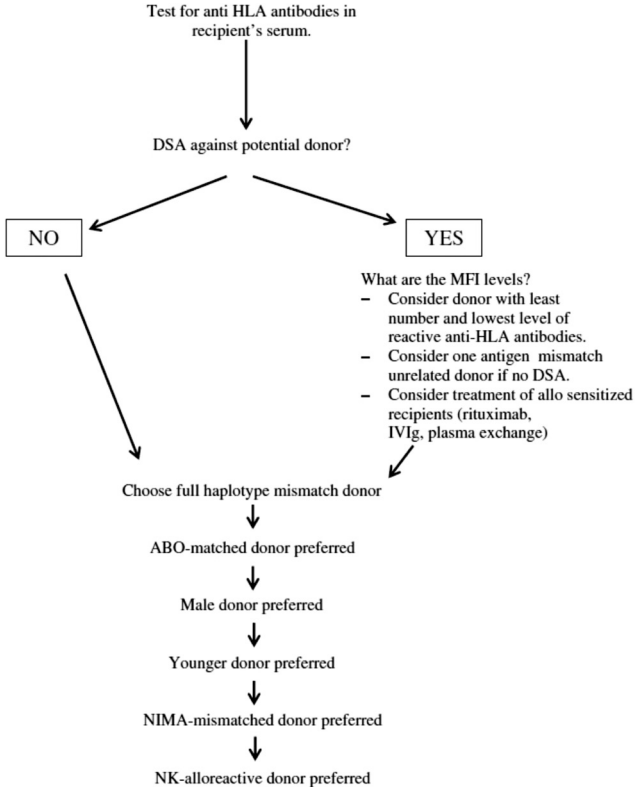

Figure 1. Proposed algorithm for donor selection in haploidentical stem cell transplantation. DSA indicates donor-specific anti-HLA antibodies; MFI: median fluorescence intensity, NIMA: non-inherited maternal antigens, NK: natural killer. Reproduced from Ciurea and Champlin with permission (32).

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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