EUROPEAN HEMATOLOGY ASSOCIATION
Ferrata Storti Foundation

Haematologica 2017
Volume 102(11):1810-1822

Haploidentical hematopoietic cell transplantation for adult acute myeloid leukemia: a position statement from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

Catherine J Lee,[1] Bipin N Savani,[2] Mohamad Mohty,[3] Myriam Labopin,[3] Annalisa Ruggeri,[3] Christoph Schmid,[4] Frédéric Baron,[5] Jordi Esteve,[6] Norbert C Gorin,[7] Sebastian Giebel,[8] Fabio Ciceri[9] and Arnon Nagler[3,10]

[1]Utah Blood and Marrow Transplant Program, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [2]Vanderbilt University Medical Center, Nashville, TN, USA; [3]Department of Hematology, Saint-Antoine Hospital, INSERM, Paris, France; [4]Klinikum Augsburg, Department of Hematology and Oncology, University of Munich, Augsburg, Germany; [5]Department of Medicine, Division of Hematology, University of Liège, Belgium; [6]Department of Hematology, Hospital Clinic, IDIBAPS, Barcelona, Spain; [7]Department of Hematology, Saint-Antoine Hospital, APHP and University UPMC, Paris, France; [8]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland; [9]Hematology, IRCCS San Raffaele Scientific Institute, Milan, Italy and [10]Hematology Division, Chaim Sheba Medical Center, Tel Hashomer, Israel

ABSTRACT

Allogeneic blood or marrow hematopoietic cell transplantation continues to be the most potent anti-leukemic treatment for adult patients with standard, high-risk, or chemo-refractory acute myeloid leukemia. Until recently, this procedure was generally limited to those recipients who had an available matched-sibling donor or matched-unrelated donor. Technical advances in graft cell processing and manipulation, control of bidirectional T cell alloreactivity, graft-*versus*-host disease prophylaxis, and other supportive measures in haploidentical transplantation now enable nearly all patients with acute myeloid leukemia to benefit from the graft-*versus*-leukemia effect with substantial reduction in procedure-related mortality. Over recent years, haploidentical donors have been increasingly adopted as a valid donor source in allogeneic hematopoietic cell transplantation for acute myeloid leukemia in the absence of an HLA-matched donor. Among centers of the European Society for Blood and Marrow Transplantation, the use of haploidentical related donor transplantation has increased by 250% since 2010, and 291% since 2005. On behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation, we summarize recent utilization trends in haploidentical transplantation for acute myeloid leukemia and describe the transformative changes in haploidentical hematopoietic cell transplantation techniques over the past decade, which have led to the current widespread use of this procedure. Furthermore, we review the efficacy of haploidentical hematopoietic cell transplantation for acute myeloid leukemia from available studies, including preliminary comparative studies, and bring attention to remaining unanswered questions and directions for future research. We conclude this report with our recommendations for the role of haploidentical hematopoietic cell transplantation in acute myeloid leukemia.

Correspondence:
bipin.savani@vanderbilt.edu

Received: July 9, 2017.
Accepted: September 5, 2017.
Pre-published: September 7, 2017.

doi:10.3324/haematol.2017.176107

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/102/11/1810

©2017 Ferrata Storti Foundation

Material published in Haematologica is covered by copyright. All rights are reserved to the Ferrata Storti Foundation. Use of published material is allowed under the following terms and conditions: https://creativecommons.org/licenses/by-nc/4.0/legalcode. Copies of published material are allowed for personal or internal use. Sharing published material for non-commercial purposes is subject to the following conditions: https://creativecommons.org/licenses/by-nc/4.0/legalcode, sect. 3. Reproducing and sharing published material for commercial purposes is not allowed without permission in writing from the publisher.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative therapy for acute myeloid leukemia (AML), with 3- to 5-year overall survival (OS) rates ranging from 23% to 88%[1-3] depending on the AML risk profile, stage, and the presence or absence of minimal residual disease (MRD). AML continues to be the primary indication for allogeneic HCT, and the number of these procedures performed for AML among the European Society for Blood and Marrow Transplantation (EBMT) centers has steadily increased over the past decade, with the most recent report showing a record number of 6,189 allogeneic HCT performed in 2015 compared to 3,946 in 2010.[4,5] In addition to the development of reduced-intensity (RI) conditioning regimens, thereby extending the use of allogeneic HCT for AML patients above the age of 60 or for those with co-morbidities, the significant growth of allogeneic HCT for AML is a result of the increased availability of alternative donors, particularly haploidentical family donors.

While a HLA-matched sibling donor (MSD) remains the preferred donor choice for optimal transplant outcomes, in reality, approximately only 30% of patients from Western countries have such a donor, therefore 70% of patients require an unrelated donor source.[6,7] Interestingly, a recent analysis using population data from the USA has challenged this well-accepted sibling match probability and describes a variation in rates ranging between 13% to 51%.[8] Perhaps more alarming is the finding of the effect of a 40-year decline in USA birth rates on decreased availability of a MSD for transplant-eligible patients. As such, the current generation of young adults (18 to 44 years) will be 1.5 times less likely to find a MSD during the peak need for HCT (at around 61 years of age) compared to their current adult counterparts (aged 45 to 64 years).[8] It is expected that a similar evolution in MSD accessibility is occurring in Western Europe as total fertility rates remain low.[9] These changes highlight the upcoming demand for and utilization of alternative donor sources.

Alternative donor options include HLA-matched unrelated donors (MUD), partially HLA-mismatched unrelated donors (MMUD), single or double umbilical cord blood units (sUCB or dUCB), and haploidentical (haplo) family donors. While MUD have traditionally been considered to be the next preferred donor following a MSD, the success of finding an 8/8 HLA MUD depends on race. While Caucasians have an approximately 75% likelihood of finding an 8/8 MUD, the probability falls to less than 20% for patients of African descent or other ethnic minorities.[7,10] Furthermore, differences in laws for donor selection and recruitment among different countries limit or delay the acquisition of a MUD.[10] The use of an unrelated donor or UCB product with a mismatch at one or two HLA loci expands the accessibility of HCT to the vast majority of patients, however, this is at the cost of an increased risk of poor transplant outcomes and/or increased expense, particularly with the use of UCB cells.

Over recent years, haploidentical donors have been increasingly adopted as a valid source of donor cells for allogeneic HCT of AML in the absence of an HLA-matched donor.[4,11] A haploidentical related donor is defined by the sharing of one haplotype (or a single identical copy of chromosome 6) with the patient containing the HLA region involving class I and class II histocompatibility genes. However, a haploidentical family donor may be greater than half-matched and have common alleles on the unshared haplotype (mismatched related donor). The most recent EBMT activity survey report described haploidentical donors as a family member with two or more loci mismatch within the loci HLA-A, -B, -C, -DRB1 and-DQB1.[4] Among centers of the EBMT, the use of haploidentical transplantation (haploHCT) for malignant and non-malignant disorders has surged by 250% since the year 2010, and by 291% since 2005. In 2010, 802 haploHCT were performed, and this number increased to 1,571 in 2013, followed by 2,012 haploHCT in 2015.[4,11] The highest utilization for haploHCT in 2015 was seen in myeloid malignancies (n=1,008), and the majority of these patients had a diagnosis of AML (n=735), with an equal proportion of patients in first complete remission (CR1) or more advanced disease (Figure 1). In contrast, the utilization of unrelated umbilical cord blood transplantation (UCBT) has sharply declined for myeloid and lymphoid malignancies.[4] This apparent preference for haploidentical donors is a result of improvements in conditioning regimens combined with new strategies to diminish the risk of graft-*versus*-host disease (GvHD) associated with one haplotype mismatched donors that have resulted in favorable clinical outcomes comparable to HLA-matched allogeneic HCT, compounded with the nearly universal and immediate availability of the donor and ease of recurrent stem cell collections for repeat cellular infusions. The ability to have rapid access to a haploidentical donor is a crucial benefit for patients with high-risk AML, as a delay in transplantation due to donor issues can result in poor outcomes.

On behalf of the Acute Leukemia Working Party (ALWP) of the EBMT, herein we aim to first describe the early strategies used in haploidentical transplantation and the pivotal developments that have made its use universal and available to nearly all patients requiring hematopoietic cell transplantation. We then summarize the evidence from available studies, evaluating its efficacy in AML, including preliminary non-comparative and comparative studies of haploHCT with other alternative donor transplants, and lastly, discuss future directions for research.

Early experiences in haploidentical transplantation

Initial experiences with unmodified bone marrow (BM) haploidentical HCT in acute leukemias generated poor outcomes as a consequence of intense bi-directional T cell alloreactivity associated with HLA-mismatches. Limited success was primarily related to delayed engraftment, graft failure, and acute graft-*versus*-host disease (aGvHD).[12-15] In order to overcome these challenges, several alternative strategies were developed. In 1993, investigators from the University of Perugia pioneered a strategy of T cell-depletion (TCD) with *ex vivo* $CD34^+$ cell selection and *in vivo* antithymocyte globulins (ATG) administration as sole prophylaxis for GvHD, accompanied by infusion of a large number of $CD34^+$ cells following intensive myeloablative and immunosuppressive conditioning, with the rationale that this strategy would help promote engraftment and decrease graft failure (Figure 2A). "Mega-doses" of stem cells were obtained by combining TCD BM with granulocyte colony-stimulating factor (G-CSF) mobilized peripher-

al blood stem cells (PBSC).[16-18] With additional modifications, 95% of patients with acute leukemia (AL) achieved primary engraftment, and aGvHD and chronic GvHD (cGvHD) were minimal. With more than 15 years of follow-up, the relapse incidence (RI) was 17% in patients with AML who were transplanted in any complete remission (CR), while the 17-year disease-free survival (DFS) rate was 43%.[19,20] In addition to a highly myeloablative regimen, the emergence of natural killer (NK) cell alloreactions following transplantation may explain the decreased incidence of relapse and improved survival.[21-24] Despite the success of the anti-leukemic effects of this strategy, TCD haploHCT was associated with high transplant-related mortality (TRM) of up to 40% mainly due to a delay in immune recovery and life-threatening infections.[18,19] Findings from an EBMT retrospective analysis of 173 adults with *de novo* AL who received a TCD haploidentical HCT in Europe showed similar outcomes, including high engraftment rate, negligible GvHD, and high TRM.[25] To circumvent the pitfalls associated with TCD haploHCT, other forms of T-cell cellular therapy were exploited, including selective T-cell-depletion,[26,27] adoptive transfer of donor T cells following transplant,[28] selective T-cell add-backs[29-32] and gene-modified donor T cells.[33]

Post-transplant cyclophosphamide: a pivotal point in haploidentical transplantation

The rationale behind the use of post-transplantation cyclophosphamide (PTCy) stems from early preclinical studies demonstrating its role in targeting alloreactive T cells and reducing GvHD when given within a narrow window following allografting.[34-39] Furthermore, the finding of preserved hematopoietic stem and progenitor cells (and in later work, regulatory T cells[40]) when exposed to cyclophosphamide owing to the high expression of aldehyde dehydrogenase,[41,42] gave rise to the first-in-human clinical trial at Johns Hopkins Hospital in 1999. Thirteen patients with high-risk hematologic malignancies underwent T cell-replete (TCR) haploidentical bone marrow transplantation (haploBMT) using a non-myeloablative (NMA) conditioning regimen consisting of fludarabine and low-dose total body irradiation (TBI), as well as 50 mg/kg of cyclophosphamide on day + 3 post-transplant, followed by tacrolimus and mycophenolic mofetil (MMF) on day + 4 for GvHD prophylaxis. Owing to a high rate of graft rejection (2 out of the first 3 patients), cyclophosphamide 14.5 mg/kg was introduced into the conditioning regimen. This adaptation resulted in an 80% primary

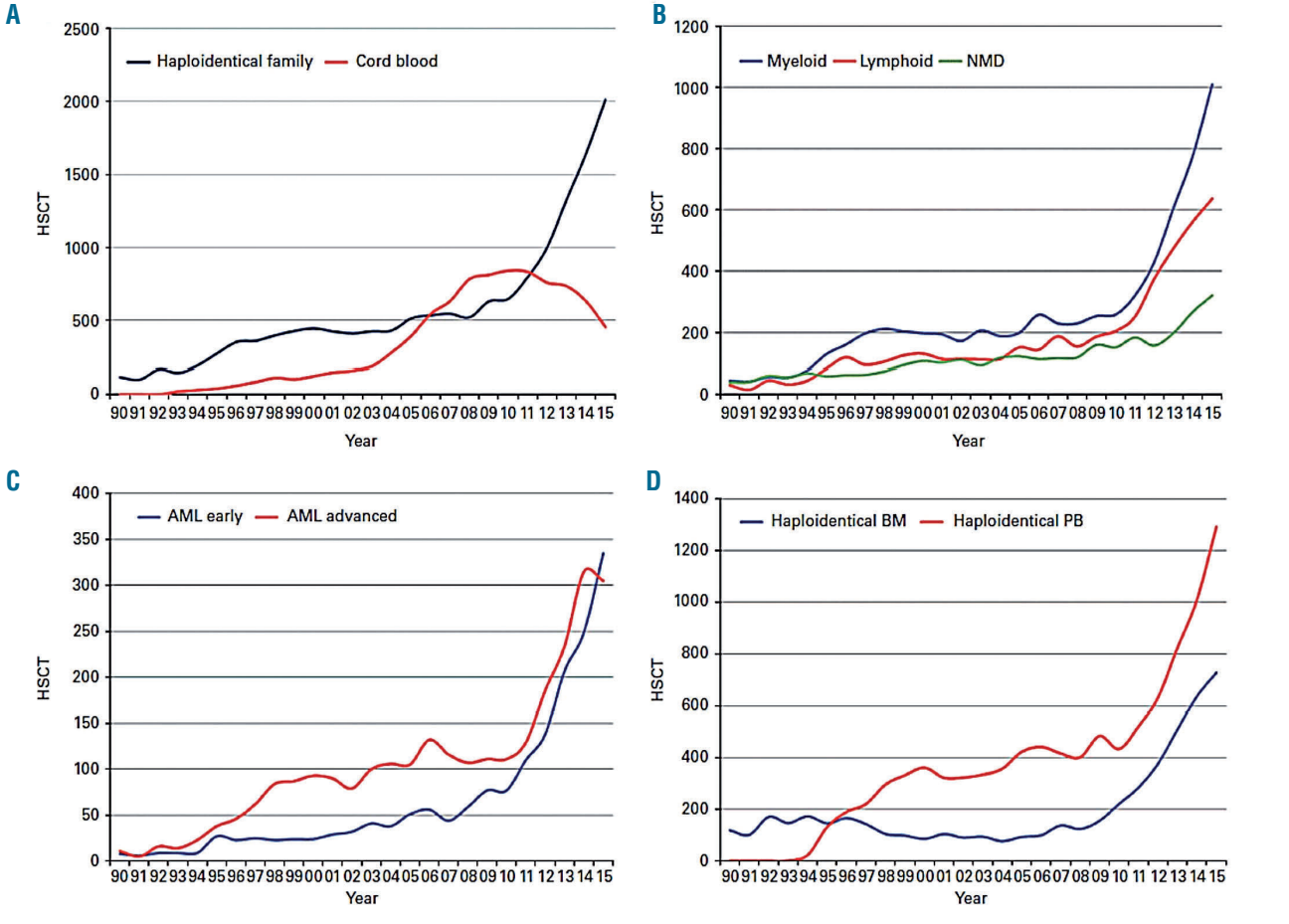

Figure 1. Trends in haploidentical HCT in Europe between 1990-2015. (A) Increasing use to haploidentical family HCT from cord blood HCT. (B) Increasing use of haploidentical HCT by main disease group. (C) Similar increase in rates of haploidentical HCT for AML early disease and AML advanced disease. (D) Haploidentical HCT by cell source; bone marrow (BM) *versus* peripheral blood (PB). Adapted from Passweg *et al.*[4] used under theCreative Commons License. AML: acute myeloid leukemia; HSCT: hematopoietic stem cell transplantation; NMD: non-malignant disorders.

engraftment rate (8 out of 10 patients), giving proof of concept to move into next phase studies.[45]

As the initial phase I study ultimately had a high cumulative incidence of graft failure and severe GvHD at 6 months post-transplant, Luznik *et al.*[44] modified the regimen by adding an additional dose of cyclophosphamide 50mg/kg on day + 4 post-transplant (Figure 2B). In a collaborative phase 2 trial between Hopkins and Seattle, 68 patients with AML (n= 27) received the revised regimen, and results yielded an 87% engraftment rate, one-year non-relapse mortality (NRM) and relapse of 15% and 51%, respectively, and two-year OS and event-free survival (EFS) of 36% and 26%, respectively. Additionally, the cumulative incidences (CI) of grades II-IV and grade III-IV aGvHD by day 200 were 34% and 6%, respectively. A trend towards a lower incidence of extensive cGvHD with the use of 2 doses of PTCy as compared to one dose was noted (5% *vs.* 25%, *P*=0.05). In an updated analysis of 210 recipients of NMA haploBMT, the Hopkins group reported similar outcomes.[45]

Due to the early reports of success with unmanipulated haploidentical HCT and pioneering of PTCy for prevention of GvHD, other centers, mainly in Western Europe and the USA, have favored the use of TCR grafts over TCD haploHCT.[10,46,47] Ciurea *et al.*[46] reported significantly improved 1-year NRM (16% *vs.* 42%, *P*=0.02), OS (64% *vs.* 30%, *P*=0.02) and progression-free survival (PFS) (50% *vs.* 21%, *P*=0.02) in 65 consecutive patients treated with a myeloablative TCR haploBMT with PTCy (n=32), compared to a TCD PBSC graft with ATG followed by infusion of CD34⁺ selected cells and no other post-transplantation immunosuppression (n=33). Engraftment rate and grade II-IV aGvHD were not significantly different, whereas cGvHD was significantly lower in patients treated with a TCR graft. In conclusion, given the ease of donor acquisition and administration of PTCy-based protocols alongside the favorable results seen in patients with high-risk hematologic malignancies, more investigation into the role of haploHCT in the early steps of decisional algorithms for the treatment of acute leukemias is ongoing.

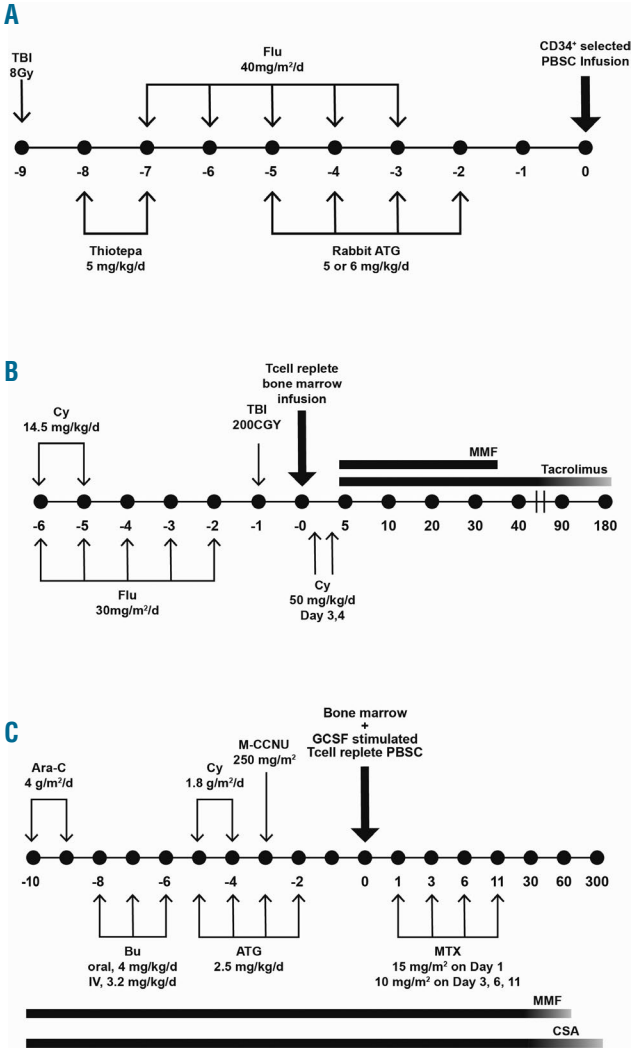

Figure 2. Commonly used platforms used in haploidentical-related transplantation.[111] (A) University of Perugia: myeloablative conditioning and T cell-depletion with "megadose" CD34⁺ cell allografts. (B) Johns Hopkins: non-myeloablative conditioning with high-dose, post-transplantation cyclophosphamide. (C) Peking University: myeloablative conditioning and *in vivo* T cell modulation (GIAC protocol). Panel B was adapted from Luznik *et al.*[44] used under the Creative Commons License. Ara-C: cytarabine; ATG: anti-thymocyte globulin; BM: bone marrow; Bu: busulfan; CSA: ciclosporin-A; Cy: cyclophosphamide; Flu: fludarabine; GCSF: granulocyte colony-stimulating factor; M-CCNU: semustine; MMF: mycophenolate mofetil; MTX: methotrexate; PBSC: peripheral-blood stem cell; TBI: total body irradiation.

Comparative donor studies of haploidentical transplantion for acute myeloid leukemia

Haploidentical *versus* matched sibling or unrelated donor transplantation

At present there are no prospective randomized comparisons of transplantations using a haploidentical donor *versus* a MSD or MUD for AML. Based on several non-randomized comparative studies evaluating transplantation outcomes following haploidentical transplantation with post-transplant cyclophosphamide or other *in vivo* T cell-depletion methods,[10,48-57] the combined data suggest similar outcomes for haploHCT compared with MSD and MUD HCT. Table 1 summarizes the available comparative studies of haploHCT with PTCy platform *versus* MSD or MUD HCT. In one of the earliest studies of haploHCT with PTCy, Bashey *et al.*[49] demonstrated equivalent primary outcomes of 271 patients with a variety of hematologic malignancies (~ 34% AML), who contemporaneously underwent a T cell-replete haploidentical MSD or MUD transplant. However, post-relapse survival at 12 months was unexpectedly lower compared to a well-matched MSD or MUD HCT (17% *vs.* 67% *vs.* 63%, *P*<0.001). In an updated cohort of 475 patients (~ 36% AML) and median follow-up of 45 months, these investigators again reported non-significant differences between haplo, MSD, and MUD transplants in DFS (54% *vs.* 56% *vs.* 50%), OS (57% *vs.* 72% *vs.* 59%), CI of NRM (17% *vs.* 14% *vs.* 16%), and relapse (29% *vs.* 30% *vs.* 34%) at 2 years after transplantation. The CIs of grade II-IV aGvHD were not significantly different between haplo and MUD HCT, however, haploHCT was associated with a significantly higher incidence of aGvHD compared to MSD (*P*=0.005 for grade II-IV). The 2-year CI of moderate-severe cGvHD was also significantly lower in haploHCT than in MSD or MUD HCT recipients (31% *vs.* 44% *vs.* 47%, *P*=<0.05),

and showed a similar trend for patients receiving a PBSC graft only.[50] In another contemporaneously treated cohort of 227 patients with AML/myelodysplastic syndrome (MDS), Di Stasi *et al.*[51] reported superimposable survival curves between haplo and 10/10 HLA MUD HCT, a non-significant improvement in outcomes with MSD HCT and a similar CI of GvHD across all donor groups.

In the largest study carried out in the USA focusing on AML, Ciurea *et al.*[48] utilized the Center for International Blood and Marrow Transplant Research (CIBMTR) registry data and reported comparable 3-year OS following haploidentical (n=192) and 8/8 HLA matched MUD HCT (n=1982) in patients with AML in various disease stages (CR1, CR2, and more advanced) who received either a myeloablative (MA) (45% *vs.* 50%, *P*=0.38) or RI (46% *vs.* 44%, *P*=0.71) conditioning regimen. Further subset analysis revealed no differences in 3-year NRM (14% *vs.* 20%, *P*=0.14) or relapse (44% *vs.* 39%, *P*=0.37) by donor type in the MA cohort, however, there was a significant decrease in 3-year NRM (9% *vs.* 23%, *P*=0.0001) and increase in relapse (58% *vs.* 42%, *P*=0.006) in the RI group. In both cohorts, 3-month grade II-IV and grade III-IV aGvHD, and 3-year cGvHD were lower after haploidentical compared with MUD transplants (MA: grade II-IV aGvHD: 16% *vs.* 33%, *P*<0.0001; grade III-IV aGvHD: 7% *vs.* 13%, *P*=0.02; cGvHD: 30% *vs.* 53%, *P*<0.0001; RI: grade II-IV aGvHD: 19% *vs.* 28%, *P*=0.05; grade III-IV aGvHD: 2% *vs.* 11%, *P*<0.0001; cGvHD: 33% *vs.* 52%, *P*=0.002). In this study, the majority of recipients of haploHCT received a BM graft, whereas PBSC were predominantly utilized in MUD HCT. Owing to the limitations inherent in an observational registry study, the investigators could not assess the impact of the donor source of stem cells on clinical outcomes. To address this question, Rashidi *et al.*[52] reported results from a single-center retrospective analysis of 140 patients who underwent a haploHCT (n=52) or MUD HCT (n=88) with PBSC. This group showed a significantly faster neutrophil and platelet recovery in the MUD

Table 1. Comparative studies of haploidentical HCT with PTCy *versus* matched donor HCT.

Author	Disease, no of pts. (AML %)	Condition Intensity (%)	Graft Source (%)	Donor Type (%)	Engraft (%)	aGvHD II-IV (d)	aGvHD III-IV (d)	cGvHD (year)	OS (year)	DFS (year)	Relapse (year)	NRM (year)
Bashey *et al.*[49]	All, 271 (34)	MA (50) RI (50)	BM (17) PB (83) Both (<1)	Haplo (20)	98	30% (d180)	11% (d180)	4% (2)	64% (2)	60% (2)	33% (2)	7% (2)
				MSD (43)	97.5	27% (*P*=NS)	8% (*P*=NS)	11% (*P*=0.062)	76% (*P*=NS)	53% (*P*=NS)	34% (*P*=NS)	13% (*P*=NS)
				MUD (37)	98	39% (*P*=NS)	11% (*P*=NS)	12% (*P*<0.05)	67% (*P*=NS)	52% (*P*=NS)	34% (*P*=NS)	16% (*P*=NS)
Di Stasi *et al.*[51]	AML/MDS, 227 (85)	RI	BM (37) PB (63)	Haplo (14)	97	29% (d100)	0% (d100)	11% (3)	66% (3)	30% (3)	33% (1)	24% (1)
				MSD (38)	99	31%	11%	31%	56%[a] (P=0.646)	36%	28%	20%
				MUD (48)	96	29% (*P*=0.709)	6% (*P*=0.044)	21% (*P*=0.125)		27% (*P*=0.12)	23% (*P*=0.75)	35% (*P*=0.099)
Ciurea *et al.*[48]	AML, 1349 (100)	MA	BM (23) PB (77)	Haplo (8)	90	16% (d90)	7% (d90)	30% (3)	45 (3)	NR	44% (3)	14% (3)
				MUD (92)	97	33% (*P* <0.0001)	13% (*P*=0.02)	53% (*P*<0.0001)	50 (*P*=0.38)		39% (*P*=0.37)	20% (*P*=0.14)
Ciurea *et al.*[48]	AML, 825 (100)	RI	BM (19) PB (81)	Haplo (11)	93	19% (d90)	2% (d90)	34% (3)	46 (3)	NR	58% (3)	9% (3)
				MUD (89)	96	28% (*P* =0.05)	11% (P<0.0001)	52% (*P*=0.002)	44 (*P*=0.71)		42% (*P*=0.006)	23% (*P*=0.0001)
Bashey *et al.*[50]	All, 475 (36)	MA (49) RI (51)	BM (21) PB (79)	Haplo (24)	97	41% (d180)	17% (d180)	31% (2)	57% (2)	54% (2)	29% (2)	17% (2)
				MSD (38)	98	21% (*P*=0.005)	9% (*P*=0.054)	44% (*P*=0.032)	72% (*P*=0.02)	56% (*P*=NS)	30% (*P*=NS)	14% (*P*=NS)
				MUD (38)	98	48% (*P*=NS)	18% (*P*=NS)	47% (*P*=0.004)	59% (*P*=NS)	50% (*P*=NS)	34% (*P*=NS)	16% (*P*=NS)
Rashidi *et al.*[52]	AML, 140	MA (44) RI (56)	PB (100)	Haplo (37)	100	40% (d180)	25% (d180)	10% (1.5)	42 (1.5)	NR	29% (1.5)	27% (1.5)
				MUD (63)	90	36% (*P*=0.51)	25% (*P*=0.79)	9% (*P*=0.91)	37 (*P*=0.17)		43% (*P*=0.08)	27% (*P*=0.54)
How *et al.*[53]	AML, 99	MA (72) RI (28)	BM (99) PB (1)	Haplo (24)	83	58% (d100)	28% (d100)	10% (1)	36% (2)	NR	33% (1)	26% (2)
				MSD (32)	91	36%	23%	10%	28%		28%	42%
				UD (43)[b]	91	57% (*P*=0.11)	30% (*P*=0.74)	15% (*P*=0.61)	29% (*P*=0.75)		48% (*P*=0.40)	29% (*P*=0.49)
Rashidi *et al.*[55]	AML, 83	MA (42) RI (58)	PB (100)	Haplo (75)	87	40% (d180)	NR	6% (1)	53% (1)	NR	31% (1)	22% (1)
				MD (25)[c]	100	19% (*P*=0.07)		5% (*P*=0.86)	58% (*P*=0.31)		26% (*P*=0.70)	16% (*P*=0.30)

[a]Represents combined MSD and MUD transplant group. [b]Represents MUD (n=35), partially mismatched (n=6); mismatched (n=2). [c]Represents combined MSD and MUD transplant group. aGvHD, acute graft-*versus*-host disease; AML: acute myeloid leukemia; BM: bone marrow; cGvHD: chronic graft-*versus*-host-disease; d: day; DFS: disease-free survival; haplo: haploidentical; MA: myeloablative; MD: matched donor; MDS: myelodysplastic syndrome; MSD: matched sibling donor; MUD: matched unrelated donor; NRM: non-relapse mortality; NR: not reported; NS: not significant; OS: overall survival; PB: peripheral blood; RI: reduced-intensity; UD: unrelated donor; yr: year.

group, but no statistically significant difference in OS, NRM, aGvHD or cGvHD at 1.5 years. Lastly, the refined disease risk index (DRI) developed by Armand and colleagues[58,59] in order to help stratify outcomes based upon disease risk and stage has been used to compare the effects of the graft-*versus*-tumor response mediated by NMA haploBMT with PTCy against historical outcomes in the setting of HLA-matched donor HCT following RI conditioning.[60] Risk-stratified disease and their associated survival outcomes appeared similar between the two groups. For example, 3-year PFS estimates in the low-, intermediate-, and high/very high-risk patient groups following NMA haploBMT with PTCy were 65%, 37%, and 22%, respectively, and 66%, 31%, and 15% in the original DRI study cohort of recipients of RI HLA-matched donor transplantation.[60]

The viability of T cell-replete haploidentical HCT with post-transplantation cyclophosphamide in patients with active AML has also been described. How *et al.*[53] compared outcomes of 99 patients who received either a MSD (n=32), unrelated donor (all unrelated, n=43; MUD, n=35), or a haploidentical related (n=24) donor transplantation for active AML, defined by ≥5% blasts in the pre-transplantation BM, persistent cytogenetics, or extramedullary disease. With a median follow-up of 18 months, no statistically significant differences between MSD, unrelated donor, and haploidentical donor HCT in 1- and 2-year OS were identified (1 yr: 28% *vs.* 41% *vs.* 45%; 2 yr: 28% *vs.* 29% *vs.* 36%, *P*=0.75), EFS (1 yr: 27% *vs.* 28% *vs.* 39%; 2 yr: 18% *vs.* 22% *vs.* 23%, *P*=0.93), TRM (1 yr: 42% *vs.* 23% *vs.* 26%; 2 yr: 42% *vs.* 29% *vs.* 26%, *P*=0.49), or 1-year relapse (28% *vs.* 48% *vs.* 33%, *P*=0.40). Similarly, the CI of grades III-IV aGvHD at day 100 (23% *vs.* 30% *vs.* 28%, *P*=0.74) and severe cGvHD at 1 year (10% *vs.* 15% *vs.* 10%, *P*=0.61) were comparable. Although not evaluated in a comparative donor study, RI T cell-replete haploHCT incorporating donor change and utilizing PTCy for postgrafting immunosuppression has also been successfully used for patients with AL relapsing after a first autologous or allogeneic transplantation.[61] These results preliminarily support the decision to use a haploidentical related donor source in transplantation of patients with active AML or relapsed AML after first transplantation, as both of these patient populations have an urgent indication to proceed to transplantation and may have a readily available haploidentical family donor.

The ALWP of the EBMT have also published results of several large multi-center comparative studies using EBMT registry data (Table 2). In the first retrospective comparative analysis of 10,679 patients with AL who received allogeneic HCT from a MSD or a haploidentical donor, Ringden *et al.*[62] sought to determine whether a stronger graft-*versus*-leukemia (GvL) effect is exerted with T cell-deplete or T cell-replete haploidentical transplantation due to the presence of mismatched major HLA antigens on leukemic cells. The investigators determined no difference in the probability of relapse between recipients of haploidentical and MSD grafts. In a more recent study, Salvatore *et al.*[56] compared outcomes of T cell-replete haploHCT (n=185) to those from MSD HCT (n=2,469) among 2,654 adults with intermediate-/high-risk AML in first CR. GvHD prophylaxis consisted of PTCy in 74% of patients and ATG in 26%. In multivariate analyses of patients with intermediate-risk AML, haploHCT was associated with reduced 2-year leukemia-free survival (LFS), OS and GvHD-free, relapse-free survival (GRFS), and higher NRM as compared to MSD HCT. In high-risk AML patients, 2-year RI was lower in haploHCT, however, no other differences were observed in NRM, LFS, OS, and GRFS.[56] In a separate registry study which focused on 6,545 patients with poor-risk AML in CR1, Versluis *et al.*[57] reported similar 2-year OS following MSD (n=3,511) with 10/10 MUD (n=1,959) and haploHCT (n=193) (hazard ratio [HR], 0.99 and 1.12, respectively), whereas both 9/10 MUD (n =549) and UCB (n=333) grafts were associated with inferior OS (HR, 1.23, *P*=0.005; and HR, 1.54, *P*<0.001, respectively). Although the RI was decreased for 10/10 MUD (HR, 0.74, *P*<0.001) and haplo (HR, 0.60, *P*=0.001) compared with MSD HCT, NRM was significantly higher. Lastly, Piemontese *et al.*[54] described clinical outcomes from T cell-replete haploHCT *versus* allogeneic transplants from 10/10 HLA matched and 9/10 HLA mismatched unrelated donors (MMUD) for adult patients with *de novo* AL in CR1/CR2. In this cohort, 265 patients (AML, n=176) received a haploHCT, 2,490 patients (AML, n=1,645) received a 10/10 MUD, and 813 patients (AML, n=510) received a MMUD transplant. Post-transplant cyclophosphamide was used as GvHD prophylaxis in 40% of haploHCT. Among patients with AML, 3-year LFS, OS, and NRM were significantly improved in 10/10 MUD compared to haploHCT, but there was no difference in GRFS, grade II-IV aGvHD or cGvHD. Further, no differences were found in GvHD or survival outcomes between 9/10 MMUD HCT and haploHCT. Based on the collective data, outcomes from haploidentical transplantation are encouraging, however, a larger cohort, longer follow-up period, and prospective comparative donor analyses are needed in order to firmly establish its place in the hierarchy of alternative donors. At this time, the ALWP-EBMT supports a 10/10 MUD as the best donor option in the absence of a MSD, and further supports the use of a haploidentical donor or 9/10 MMUD as equally viable alternatives in the absence of a fully matched donor, or in the case of the need for an urgent transplant.

Haploidentical *versus* UCBT

Single- and multi-center studies have also shown the value of single or double UCBT for AML in the setting of an urgent need for transplant and lack of an HLA-matched sibling or an unacceptable unrelated donor.[63-68] Therefore, early comparative studies of alternative donor sources focused on examining differences in clinical outcomes with the use of haploidentical or UCB as sources of stem cells (Figure 3).[65,69-72] In the earliest retrospective comparative study, the Eurocord group, in collaboration with the ALWP-EBMT, reported outcomes on 220 adult recipients who received T cell-deplete haploHCT with PBSC (n=154) or unrelated single or double UCBT (n=66) for AML. The 2-year incidences of relapse, TRM and LFS were not statistically different after haploHCT or UCBT, however, UCBT was associated with delayed neutrophil recovery and a higher incidence of aGvHD.[69] In another large EBMT observational study of 918 AML patients (haplo, n=158; UCBT, n=558), Ruggeri *et al.*[71] demonstrated similar findings of a comparable RI (HR=0.95, *P*=0.76), NRM (HR=1.16, *P*=0.47), and LFS (HR=0.78, *P*=0.78) between unmanipulated haploHCT and UCBT. While grade II-IV and grade III-IV aGvHD were similar between the two groups, the CI of cGvHD was less in the UCBT cohort (HR=0.63, *P*=0.008).

In order to study the reproducibility of the results found in retrospective analyses, the USA Blood and Marrow Transplantation Clinical Trials Network (BMT CTN) conducted two parallel multicenter prospective clinical trials focused on outcomes associated with unmanipulated related haplo-BM graft with PTCy (n=50) and dUCBT (n=50)

Table 2. Published ALWP-EBMT studies of haploidentical transplantation in adults with AML.

Reference (year)	Study Objective	Conclusions
Rocha *et al.*[69] (2005)	Retrospective comparative analysis of outcomes of 364 adult patients with AML/ALL receiving either UCBT *versus* T cell-depleted PB haploHCT between 1998-2002.	In AML, no difference between groups in relapse, TRM, and LFS. UCBT had increased grade II-IV aGvHD.
Ciceri *et al.*[25] (2008)	Retrospective analysis of outcomes of 266 adult patients with *de novo* acute AML/ALL receiving T cell-depleted PB haploHCT between 1995-2004.	Engraftment occurred in 91% of the patents; 2-year LFS was 48% ± 10% for patients with AML in CR1; 21% ± 5% in ≥ CR2; and 1% ± 1% in non-remission; GvHD was minimal.
Gorin *et al.*[110] (2015)	Matched pair analysis of outcomes of 188 T cell-replete haploHCT and 356 autologous transplants (ASCT) in adult patients with acute leukemia between 2007-2012.	Haploidentical centers were divided into "expert" *vs.* "regular" based on the number of haploHCT performed. NRM was higher among all haploHCT compared to ASCT. LFS and OS were higher following ASCT compared to haploHCT in regular centers and similar
Ruggeri *et al.*[71] (2015)	Retrospective comparative analysis of outcomes of 1,446 adult patients with *de novo A*ML/ALL receiving either UCBT *versus* unmanipulated haploHCT between 2007-2012.	In multivariate analysis of the AML group, UCBT was associated with lower cGvHD. No significant differences in relapse, NRM, and LFS between the two groups.
Piemontese et al.10 (2015)	Retrospective analysis of outcomes of 229 adult patients with *de novo* AML/ALL in CR or non-remission who received an unmanipulated haploHCT between 2007-2011.	Engraftment occurred in 93% of the patents; For the total group: 3-year relapse, LFS, OS and NRM was 42%, 30%, 37%, and 28%. 100-day CI of Grade II-IV aGvHD (32%) and 3-year CI of cGvHD (34%) were similar to historical outcomes of MSD HCT.
Ringden *et al.*[62] (2016)	Retrospective comparative analysis of relapse and survival outcomes of 10,679 adult patients with AML/ALL receiving MSD HCT versus T cell-replete or deplete haploHCT between 2007-2012.	No difference in relapse between MSD and haploHCT groups while NRM and LFS was superior in the MSD group.
Rubio *et al.*[88] (2016)	Retrospective comparative analysis of outcomes of 696 adult patients with AML/ALL receiving T cell-replete haploHCT with RI *versus* MA conditioning regimen between 2001-2012.	Multivariable analysis in AML showed no difference in NRM, cGvHD, LFS, and OS. There was a trend toward high relapse with RI conditioning.
Sun *et al.*[82] (2016)	Retrospective one-to-one matched pair comparative study of outcomes following GIAC-based haploHCT and MA 10/10 MUD HCT in 174 patients with *de novo* intermediate-risk (based on cytogenetics) AML in CR1.	Similar 5-year LFS, OS, relapse, NRM, grade III-IV aGvHD, and cGvHD.
Ruggeri *et al.*[89] (2016)	Retrospective comparative analysis of outcomes of 451 adult patients with AML/ALL in CR1/CR2 receiving T cell-replete haploHCT with PTCy with PB *versus* BM stem cells between 2010-2014.	Multivariable analysis showed that PB was associated with increased risk of grade II-IV aGvHD. Otherwise, no significant difference in other GvHD or survival outcomes.
Piemontese *et al.*[54] (2017)	Retrospective comparative analysis of outcomes of 3,568 adult patients with *de novo* AML/ALL in CR1/CR2 who received T cell-replete haploHCT *versus* 10/10 MUD or 9/10 MMUD HCT between 2007-2013.	Weighted Cox model showed significantly higher LFS and OS in transplants from 10/10 MUD compared to haploHCT but no difference between 9/10 MMUD and haploHCT. Acute and chronic GvHD were not impacted by the donor type.
Ruggeri *et al.*[83] (2017)	Retrospective comparative analysis of outcomes of 308 adult patients with AML in CR1/CR2 who underwent T cell-replete haploHCT using PTCy *versus* ATG-based GvHD prophylaxis between 2007-2014.	HaploHCT with a PTCy-based prophylaxis produced superior LFS, GRFS, and lower incidence of GvHD and NRM compared to ATG-based prophylaxis.
Versluis *et al.*[57] (2017)	Retrospective comparative analysis of outcomes of 6,545 adult patients with poor-risk AML in CR1 receiving an allogeneic HCT using MRD *versus* 10/10 or 9/10 MUD, UCB, T cell-replete haplo-identical donor between 2000-2014.	Multivariable analysis confirmed no differential impact on OS and RFS following MRD, 10/10 MUD, or haplo HCT, and significantly worse OS with 9/10 MUD and UCB grafts. Relapse was decreased for 10/10 MUD compared to MRD and haploHCT, and NRM was significantly higher for all alternative donors compared to MRD HCT.
Salvatore *et al.*[56] (2017)	Retrospective comparative analysis of outcomes of 2,654 adult patients with int-AML or high-risk AML in CR1 receiving T cell-replete haploHCT versus MSD HCT.	Int-AML: multivariate analysis showed reduced LFS, OS, GRFS, and higher NRM after haploHCT. High-risk AML: increased grade II-IV aGvHD and lower relapse incidence with haploHCT, and similar NRM, LFS, and OS between both donor groups.
Canaani et al.96 (2017)	Retrospective comparative analysis of outcomes in 837 adult patients with AML who received ABO-matched *versus* ABO-mismatched haploHCT between 2005-2014.	Major ABO mismatching was associated with inferior day 100 engraftment, and bi-directional mismatching had increased risk of grade II-IV aGvHD. Otherwise, NRM, relapse, LFS, OS, and cGvHD were similar.

aGvHD: acute graft-*versus*-host disease; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; ASCT,: autologous stem cell transplantation; ATG: antithymocyte globulin; BM: bone marrow; cGvHD: chronic graft-*versus*-host-disease; CI: cumulative incidence; CR: complete remission; GRFS: GvHD-free, relapse-free survival; GvHD: graft-*versus*-host disease; haplo: haploidentical; HCT: hematopoietic cell transplantation; int-AML: intermediate AML; LFS: leukemia-free survival; MA: myeloablative; MMUD: mismatched unrelated donor; MRD: minimal residual disease; MSD: matched sibling donor; MUD,: matched unrelated donor; NRM: non-relapse mortality; OS: overall survival; PB: peripheral blood; PTCy: post-transplant cyclophosphamide; RFS: relapse-free survival; RI: reduced-intensity; TRM: transplant-related mortality; UCB: umbilical cord blood; UCBT: umbilical cord blood transplantation.

following identical RI conditioning regimens for patients with high-risk leukemia or lymphoma (AML: haplo, n=22; dUCB, n=29). Results from this trial successfully replicated those from single-center studies and showed no significant differences between the two modalities.[65] Furthermore, both cohorts had comparable survival rates to patients with high-risk hematologic malignancies who underwent MUD HCT with blood or marrow after RI conditioning.[73] An ongoing phase III multicenter randomized trial (*clinicaltrials.gov Identifier: 01597778*) is attempting to clarify the relative efficacies of double unrelated cord and haploidentical related BMT, and the estimated completion date of the trial is June 2019.

The Beijing experience

An alternative strategy for prevention of GvHD after T cell-replete haploidentical donor transplantation has incorporated pre-transplant ATG. The Peking University group in China pioneered an approach that used a combination of G-CSF-priming of the donor, intensified immunosuppression, ATG, and combination of T cell-replete BM plus peripheral blood as the stem cell source (GIAC protocol) (Figure 2C).[74,75] An early trial in patients with acute leukemia, including 108 AML patients, suggested encouraging GvL effects with universal engraftment, low incidence of relapse following transplantation (13 out of 108 AML patients) and 3-year relapse probabilities of 11.9% and 20.2% in the standard- and high-risk AML groups, resulting in DFS rates of 71% and 56%, respectively. While TRM at D+100 was favorable in both risk groups, the 3-year TRM in standard-risk and high-risk AML groups was 19.4% and 29.4%. The CI of grade II-IV and grade III-IV aGvHD were 45.8% and 13.4% at D+100, respectively, while the 3-year CI of total cGvHD and extensive cGvHD were 53.9% and 22.6%.[75] An updated trial including 756 patients with AL over a time period of 9 years confirmed their previous findings.[76] A subsequent comparative study in patients with AML who received the GIAC haploHCT protocol revealed a similar CI of acute and chronic GvHD, TRM, 5-year relapse and OS rates when compared to MUD HCT, but a significantly reduced incidence of 5-year relapse (14.2% *vs*. 34%, *P*=0.008) compared to MSD HCT. A superior GvL effect for high-risk leukemia was also observed in haploHCT, as 5-year relapse rates were 15.4%, 28.2%, and 49.9% in haplo, MUD (*P*=0.07), and MSD HCT, respectively (*P*=0.002).[77] Results from Wang *et al.*[78] also suggested a superior GvL effect by haploHCT compared to a matched sibling HCT in patients with high-risk AL (50 AML out of 117), whereas other studies indicated no significant difference.[79,80] In three of the four studies, grade II-IV aGvHD was significantly more frequent after haploHCT compared to MSD HCT. In the only prospective study comparing post-transplantation outcomes in 450 patients with intermediate- or high-risk AML in CR1 who received a haplo or MSD HCT, Wang *et al.*[81] demonstrated a similar CI of relapse (15% *vs.* 15%, *P*=0.98), 3-year DFS (74% *vs*. 78%, *P*=0.34), NRM (13% *vs*. 8%, *P*=0.13), and OS (79% *vs*. 82%, *P*=0.36). The CI of 100-day aGvHD and 1-year cGvHD, including severe cGvHD, was significantly higher in the haploHCT group. Owing to the lack of randomization, this comparative study suggests haploidentical HCT as a valid alternative option for this patient population for whom no matched sibling donor is available.

Due to the reported high leukemia-free survival rates associated with the Beijing strategy, the ALWP of the EBMT performed a retrospective one-to-one matched pair comparative study of outcomes following GIAC-based haploidentical HCT and myeloablative (non-TBI based) 10/10 MUD HCT in patients with *de novo* intermediate-risk (based on cytogenetics) AML in CR1.[82] Subjects were matched in age, time to transplant, and number of induction courses to reach CR1. Similar outcomes were observed between haploHCT and MUD HCT in terms of 5-year LFS (73.5% *vs.* 60.3%, *P*=0.15), OS (78.2% *vs*. 63.6%, *P*=0.15), relapse (12.7% *vs*. 24%, *P*=0.08), NRM (13.8% *vs*. 15.7%, *P*=0.96), grade III-IV aGvHD (9.2% *vs*. 9.4%, *P*=1), and cGvHD (42.5% *vs*. 34.9%, *P*=0.39). Based on this analysis, the authors concluded that the Beijing protocol is a feasible alternative to allogeneic transplantation with a 10/10 MUD.

Following several publications showing very low incidences of GvHD after ATG-based intensive immunosuppression established in the GIAC haploHCT protocol, Ruggeri *et al.*[83] compared this GvHD prophylaxis regimen to the PTCy platform in the setting of unmanipulated haploHCT for patients with various-risk AML in CR1 or CR2. A total of 308 patients were studied (PTCy, n=193; ATG, n=115), and both groups were well matched in regards to recipient and donor age, AML disease risk, disease status at transplant, and conditioning intensity. Notably, a BM stem cell source was used more frequently in the PTCy group (60.1% *vs*. 39.9%, *P*=0.01), and that cohort also had shorter follow up (18 *vs*. 36 months, *P*<0.001). At day 100, similar outcomes in grade II-V aGvHD were observed between patients receiving PTCy *versus* ATG (31% *vs*. 21%, *P*=0.07), however, grade III-IV aGvHD was significantly lower in the PTCy group (4.7% *vs*. 12.5%, *P*=0.01). The incidence of 2-year cGvHD did not differ between the two groups (33.7% *vs*. 28.3%, *P*=0.33). Multivariate analysis of NRM, LFS, OS, and GRFS also significantly favored the PTCy regimen.

Although different haploHCT methods have not been prospectively compared in a randomized fashion, the available cumulative evidence demonstrates the feasibility of haploidentical transplantation and the benefit of having a readily accessible donor, regardless of the platform used.

Ongoing research in T cell-replete haploidentical transplantation

Since the demonstration of the safety and efficacy of NMA haploHCT with PTCy, there has been increasing research interest in optimizing clinical outcomes for different patient populations through modifications of the original platform. For example, some groups have explored optimizing the anti-leukemia effects of haploHCT, particularly in high-risk or advanced AML, by intensifying the conditioning regimen or substituting BM with PBSC as the stem cell graft source, due to the concern of high relapse rates associated with NMA haploHCT and PTCy. In the former setting, several single-center non-comparative studies have reported a low risk of acute and chronic GvHD and encouraging rates of TRM and OS with myeloablative conditioning.[84-87] These observations were recently validated by the first large retrospective comparative analysis performed by the ALWP-EBMT showing similar OS, LFS, NRM, and cGvHD between MA and RI conditioning regi-

Table 3. Comparative studies of haploidentical HCT *versus* umbilical cord blood transplantation.

Author	Disease, no of pts. (AML, n)	Condition Intensity (%)	Graft Source (n)	Donor Type (no. of patients)	Engraft (%)	aGvHD II-IV (yr)	aGvHD III-IV (yr)	cGvHD (yr)	OS (yr)	DFS (yr)	Relapse (yr)	NRM (yr)
Rocha *et al.*[69]	AML, 220	NR	NR (haplo)	Haplo (154) UCB (66)	NR	5 =/- 5% 23 +/- 5% <0.0001	NR	NR	NR	24±4% (2) 30±6% (*P*=0.39)	18±3% (2) 24±5% (*P*=0.44)	58±4% 46±2% (*P*=0.23)
Brunstein *et al.*[65^]	All, 100 (AML, 51)	RI (100)	BM (50)	Haplo (50) UCB (50)	94 96	32% (d100) 40%	0% (d100) 21%	13% (1) 25%	62% (1) 54%	48% (1) 46%	45% (1) 31%	7% (1) 24%
Ruggeri *et al.*[71]	AML, 918	MA (54%) RI (46%)	BM (171) PB (78) Both (14)	Haplo (360) UCB (558)	91 84 (*P*=0.003)	27% (*) 31% (*P*=0.10)	11% (*) 12% (*P*=0.41)	29% (*) 24% (*P*=0.19)	38% (*) 42% (*P*=0.269)	32% (2) 38% (*P*=0.102)	41% (*) 32% (*P*=0.008)[α]	27% (*) 30% (*P*=0.356)
El-Cheikh *et al.*[72]	All, 150 (AML, 40)	RI (100)	BM (NR) PB (NR)	Haplo (69) UCB (81)	94 90	34% (*) 50% (*P*=0.08)	5% (*) 33% (*P*<0.0001)	6% (*) 12% (*P*=0.001)	69% (2) 45% (*P*=0.10)	65% (2) 36% (*P*=0.01)	18% (*) 38% (*P*=0.03)	18% (2) 23% (*P*=0.49)

^The data are from 2 separate but parallel multicenter phase 2 trials with identical objectives, eligibility, and clinical endpoints. The clinical outcomes should not be compared directly. * Year not reported. [α]Multivariate analysis of relapse was not statistically different between the haplo and UCB groups (HR 0.95, *P*=0.76). aGvHD: acute graft-*versus*-host disease; AML: acute myeloid leukemia; ALL: acute lymphocytic leukemia; BM: bone marrow; cGvHD, chronic graft-*versus*-host-disease; DFS: disease-free survival; haplo: haploidentical; MA: myeloablative; NRM: non-relapse mortality; NR: not reported; OS: overall survival; PB: peripheral blood; RI: reduced-intensity; UCB: umbilical cord blood; yr, year.

mens in T cell-replete haploHCT, in particular for patients with AML in CR1.[88] Multivariable analyses revealed a trend towards higher relapse incidence, with RI *versus* MA conditioning (HR 1.34, *P*=0.09), and when taken collectively the data supported the use of either high or low intensity conditioning haploHCT with PTCy in the first-line treatment of high-risk AML.[88] In this study, there was an increased risk of grade II-IV aGvHD and cGvHD independent of the conditioning regimen intensity and of the use of PTCy with the use of a PBSC graft compared to BM, but no difference was seen with regard to the incidence of NRM and other survival outcomes.[88] Ruggeri *et al.*[89] also described the use of PBSC as the sole factor associated with an increased risk of grade II-IV aGvHD (HR 2.2, 95% CI 1.27-3.9, *P*=0.005) in patients with AL, the majority of whom were transplanted with a MA regimen for AML in CR1. Otherwise, the type of stem cell graft (PBSC *vs*. BM) proved to have no significant difference on grade III-IV aGvHD, cGvHD, relapse, or survival. In line with the attempts to exploit a PBSC source, Peccatori *et al.* developed a calcineurin inhibitor-free GvHD prophylaxis based on rapamycin, mycophenolate mofetil and ATG, with the aim of promoting a fast post-transplant immune recovery with a preferential accumulation of regulatory T cells.[90] Recently, this sirolimus platform has been modified with the substitution of ATG by PTCy, which showed a significant reduction in cGvHD.[91] In the NMA haploHCT setting, both Castagna *et al.*[92] and O' Donnell *et al.*[93] reported comparable outcomes in acute and chronic GvHD, engraftment rates, NRM, and OS after haplo-BM or haplo-PBSC transplantation; however, the incidence of relapse at 1 to 3 years was significantly lower after haplo-PBSC transplant compared with haplo-BM transplants in the latter study. Other groups have also demonstrated the feasibility of NMA haploHCT with either PBSC or BM stem cells in older adults.[94,95] The significance of ABO incompatibility on outcomes after haploHCT for AML have recently been published by the ALWP-EBMT, and preliminarily demonstrate a significantly increased risk of grade II-IV aGvHD with bi-directional ABO mismatching and a lower OS rate in patients with major ABO mismatching transplanted with BM grafts.[96] Lastly, the impact of haploHCT for specific high-risk AML cytogenetic and molecular risk groups as well as the role of post-transplant cellular therapies are of interest.

The significance of pre-transplant MRD as a poor prognostic and predictive factor of outcomes after allogeneic HCT in AML has been reported.[3,97-99] For example, the Seattle group published inferior 3-year OS and relapse outcomes among AML patients receiving a myeloablative matched donor HCT with pre-transplant MRD-positive (morphologic remission) compared to MRD-negative (morphologic remission), and further demonstrated comparable outcomes to patients with active disease at the time of HCT.[3] Several other groups have studied the significance of pre-transplant MRD on a more granular level and demonstrated that the level of pre-transplant MRD may differentially impact post-transplantation outcomes[100,101] The significance of pre-transplant MRD has also been described in the setting of haploHCT.[102,103] Wang *et al.*[102] retrospectively evaluated outcomes of 255 patients with AML in CR1 or CR2. Multivariate analysis indicated failure of CR after 2 courses of induction therapy as the strongest independent prognostic factor for relapse and LFS. In subgroup analysis, positive pre-transplant MRD as compared to negative MRD also resulted in worse LFS at 3 years (76% *vs*. 52%, *P*=0.041) and CI of relapse at 2 years (10% *vs*. 35%, *P*=0.002). These results must be interpreted cautiously due to the limited patient sample (negative MRD, n=110; positive MRD, n=20). Conversely, other groups have reported no significant influence of MRD status (positive *vs*. negative) prior to haploHCT on PFS[104] or relapse[103] for patients with AML in CR1/CR2, and further hypothesize that while detectable MRD before HCT is a strong unfavorable prognostic factor, its adverse impact may be overcome by the potentially stronger GvL effects of unmanipulated haploHCT.[103]

Perspectives

Over the last two decades, the international BMT community have witnessed incredible advances in HLA-typ-

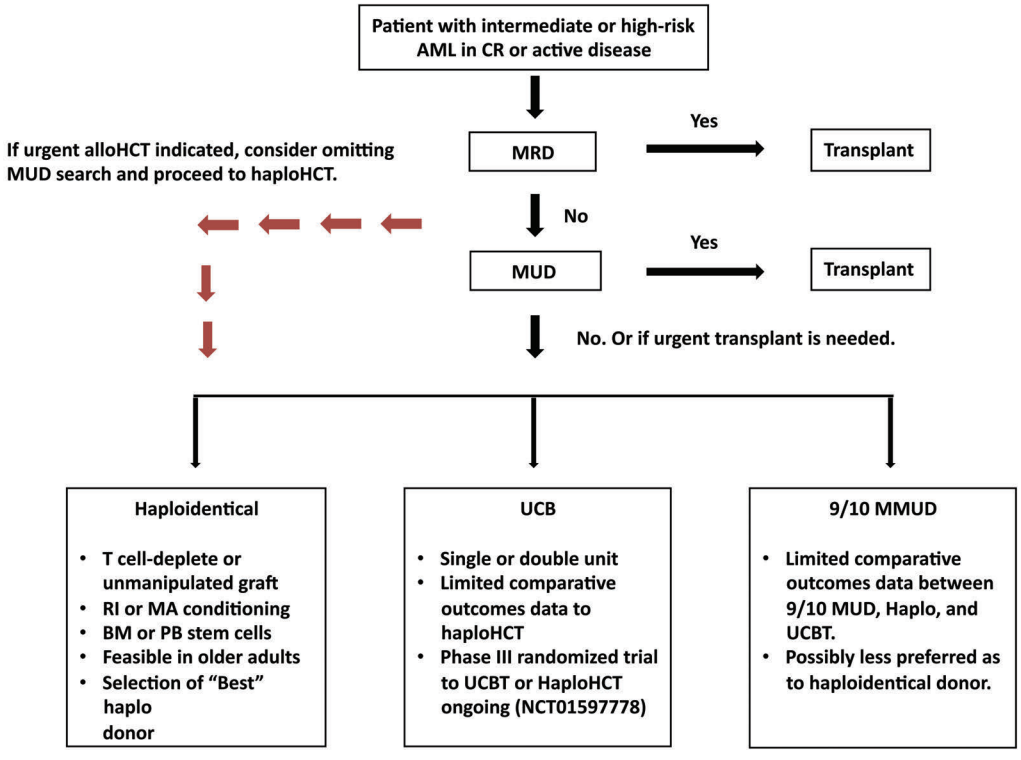

Figure 3. Recommended donor choice algorithm for adults with intermediate or high-risk AML with an indication for allogeneic HCT. AML: acute myeloid leukemia; BM: bone marrow; CR: complete remission; alloHCT: allogeneic hematopoietic cell transplantation; haploHCT: haploidentical hematopoietic cell transplantation; MMUD: mismatched unrelated donor; MRD: matched related donor; MUD: matched unrelated donor; PB: peripheral blood; UCB: umbilical cord blood; UCBT: umbilical cord blood transplantation. RI: reduced-intensity; MA: myeloablative.

ing and alternative donor transplantation strategies, such that in the present day nearly all transplant-eligible patients with AML will have an available donor. Unmanipulated haploidentical related transplantation with post-transplant cyclophosphamide has emerged as a potentially powerful strategy for the cure of AML and is the dominant haploHCT platform in Europe.[105] Other significant advantages of haploHCT with PTCy include its associated low non-relapse mortality and GvHD, ease of donor accessibility often leading to minimal length of time to transplantation, and low acquisition costs. The cost-effectiveness associated with haploHCT with PTCy may have the most appeal in developing countries, where economic resources are more limited.[105] Unmanipulated haploidentical transplantation with post-transplantation immunosuppression also shows promise in decreasing post-transplant infections and death due to infections, however, further data on immune reconstitution, infections and their related complications (i.e., hemorrhagic cystitis) among different haploHCT strategies are warranted.[106] The incidence of post-transplant cardiomyopathy secondary to GvHD prophylaxis with high-dose PTCy appears non-significant in the absence of severe infection,[107] however, further research evaluating predictive factors for cardiomyopathy following PTCy based HCT are necessary. While there has been questioning of donor-derived malignancies (DDM) associated with PTCy, a recent retrospective study by the Hopkins group showed an extremely low proportion of patients with a DDM (4 out of 789) over a 10-year period, suggesting that PTCy does not appear to increase the risk of DDM.[108] However, the authors acknowledge the short follow-up period of their study and report the need for continued close monitoring of DDMs over a longer follow-up time.

Another key issue arising in the setting of unmanipulated haploHCT is the selection of the "best" donor, as some patients will have multiple haploidentical donor candidates and donor selection may significantly impact GvHD, relapse, TRM, and survival outcomes. Owing to improved approaches of unmanipulated haploHCT with PTCy or ATG-based GvHD prophylaxis, the effects of HLA disparity have vanished, nonetheless, other donor-related variables should be considered. These include the selection of donors for whom there are no recipient donor-specific antibodies (DSA); alternatively, measures to remove DSA should be undertaken in the patient; the selection of a younger, male donor over an older, female donor due to the potential for superior survival, decreased risk of grade II-IV aGvHD and age-related clonal hematopoiesis leading to subsequent malignancies; and the selection of an ABO compatible donor, followed by a minor ABO mismatched and then a major ABO mismatched donor. Other factors to consider include donor and recipient cytomegalovirus (CMV) serostatus, NK cell alloreactivity and KIR haplotype matching, and non-inherited maternal HLA antigens (NIMA) mismatching.[109] However, more research is needed as the significance of each of these factors may change depending on the haploHCT protocol or platform used, and indeed, may vanish, due to the emergence of new variables as

haploHCT becomes increasingly utilized.

In conclusion, the growing body of literature has consistently demonstrated comparable outcomes of haploidentical donor HCT as compared to an UCB, matched sibling and unrelated donor transplantation for patients with AML. However, the available studies are nonrandomized, underpowered, and lack long-term follow-up data. Accordingly, the ALWP-EBMT endorses haploidentical transplantation as a valid post-remission therapy for high-risk AML in the absence of a matched donor or in the case of the need for an urgent transplant procedure (Figure 3). Further prospective studies randomizing haploHCT to UCBT (in the USA) or to MUD or MMUD HCT (in Europe) are ongoing, and will help to establish its position in the hierarchy of alternative donors.

Position statement from the ALWP- EBMT

- Haploidentical donor transplantation is a valid option for patients with AML lacking a matched sibling or unrelated donor.
- In certain clinical situations, especially in the case of a need for an urgent transplant procedure and lack of a MDS, a readily available haploidentical donor may be considered over initiating an unrelated donor search.
- The evidence for the superiority of haploidentical *vs*. MMUD *vs*. UCBT is insufficient, but there is the potential for a cost benefit with regard to haploHCT.
- There is insufficient evidence for the superiority of one haploidentical HCT platform over another. Economic factors, together with individual center experience, may be decisive.

References

1. Zuckerman T, Rowe JM. Transplantation in acute myeloid leukemia. Hematol Oncol Clin North Am. 2014;28(6):983-994.
2. Cornelissen JJ, Gratwohl A, Schlenk RF, et al. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. Nat Rev Clin Oncol. 2012;9(10):579-590.
3. Araki D, Wood BL, Othus M, et al. Allogeneic hematopoietic cell transplantation for acute myeloid leukemia: time to move toward a minimal residual disease-based definition of complete remission? J Clin Oncol. 2016;34(4):329-336.
4. Passweg JR, Baldomero H, Bader P, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. Bone Marrow Transplant. 2017;52(6):811-817.
5. Passweg JR, Baldomero H, Gratwohl A, et al. The EBMT activity survey: 1990-2010. Bone Marrow Transplant. 2012;47(7):906-923.
6. Tiercy JM. How to select the best available related or unrelated donor of hematopoietic stem cells? Haematologica. 2016;101(6):680-687.
7. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med. 2014;371(4):339-348.
8. Besse K, Maiers M, Confer D, Albrecht M. On modeling human leukocyte antigen-identical sibling match probability for allogeneic hematopoietic cell transplantation: estimating the need for an unrelated donor source. Biol Blood Marrow Transplant. 2016;22(3):410-417.
9. Employment, Social Affairs & Inclusion Eurostat Demography Report. European Commission. Luxembourg: Publications Office of the European Union; 2015 [updated May 2015; cited 8 August 2017]. Available from: http://ec.europa.eu/eurostat/web/population-demography-migration-projections/overview
10. Piemontese S, Ciceri F, Labopin M, et al. A survey on unmanipulated haploidentical hematopoietic stem cell transplantation in adults with acute leukemia. Leukemia. 2015;29(5):1069-1075.
11. Passweg JR, Baldomero H, Bader P, et al. Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants. Bone Marrow Transplant. 2015;50(4):476-482.
12. Beatty PG, Clift RA, Mickelson EM, et al. Marrow transplantation from related donors other than HLA-identical siblings. N Engl J Med. 1985;313(13):765-771.
13. Anasetti C, Amos D, Beatty PG, Appelbaum FR, Bensinger W, Buckner CD, et al. Effect of HLA compatibility on engraftment of bone marrow transplants in patients with leukemia or lymphoma. N Engl J Med. 1989;320(4):197-204.
14. Anasetti C, Beatty PG, Storb R, et al. Effect of HLA incompatibility on graft-versus-host disease, relapse, and survival after marrow transplantation for patients with leukemia or lymphoma. Hum Immunol. 1990;29(2):79-91.
15. Powles RL, Morgenstern GR, Kay HE, et al. Mismatched family donors for bone-marrow transplantation as treatment for acute leukaemia. Lancet. 1983;1(8325):612-615.
16. Aversa F, Tabilio A, Terenzi A, et al. Successful engraftment of T-cell-depleted haploidentical "three-loci" incompatible transplants in leukemia patients by addition of recombinant human granulocyte colony-stimulating factor-mobilized peripheral blood progenitor cells to bone marrow inoculum. Blood. 1994;84(11):3948-3955.
17. Aversa F, Tabilio A, Velardi A, et al. Treatment of high-risk acute leukemia with T-cell-depleted stem cells from related donors with one fully mismatched HLA haplotype. N Engl J Med. 1998;339(17):1186-1193.
18. Aversa F, Terenzi A, Tabilio A, et al. Full haplotype-mismatched hematopoietic stem-cell transplantation: a phase II study in patients with acute leukemia at high risk of relapse. J Clin Oncol. 2005;23(15):3447-3454.
19. Aversa F. Setting the standard in T-cell-depleted haploidentical transplantation and beyond. Best Pract Res Clin Haematol. 2011;24(3):325-329.
20. Mancusi A, Ruggeri L, Velardi A. Haploidentical hematopoietic transplantation for the cure of leukemia: from its biology to clinical translation. Blood. 2016;128(23):2616-2623.
21. Ruggeri L, Capanni M, Casucci M, et al. Role of natural killer cell alloreactivity in HLA-mismatched hematopoietic stem cell transplantation. Blood. 1999;94(1):333-339.
22. Ruggeri L, Capanni M, Urbani E, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science. 2002;295(5562):2097-2100.
23. Ruggeri L, Mancusi A, Capanni M, et al. Donor natural killer cell allorecognition of missing self in haploidentical hematopoietic transplantation for acute myeloid leukemia: challenging its predictive value. Blood. 2007;110(1):433-440.
24. Velardi A, Ruggeri L, Mancusi A, Aversa F, Christiansen FT. Natural killer cell allorecognition of missing self in allogeneic hematopoietic transplantation: a tool for immunotherapy of leukemia. Curr Opin Immunol. 2009;21(5):525-530.
25. Ciceri F, Labopin M, Aversa F, et al. A survey of fully haploidentical hematopoietic stem cell transplantation in adults with high-risk acute leukemia: a risk factor analysis of outcomes for patients in remission at transplantation. Blood. 2008;112(9):3574-3581.
26. Andre-Schmutz I, Le Deist F, Hacein-Bey-Abina S, et al. Immune reconstitution without graft-versus-host disease after haemopoietic stem-cell transplantation: a phase 1/2 study. Lancet. 2002;360(9327):130-137.
27. Amrolia PJ, Muccioli-Casadei G, Huls H, et al. Adoptive immunotherapy with allodepleted donor T-cells improves immune reconstitution after haploidentical stem cell transplantation. Blood. 2006;108(6):1797-1808.
28. Triplett BM, Shook DR, Eldridge P, et al. Rapid memory T-cell reconstitution recapitulating CD45RA-depleted haploidentical transplant graft content in patients with hematologic malignancies. Bone Marrow Transplant. 2015;50(7):968-977.
29. Hoffmann P, Ermann J, Edinger M, Fathman CG, Strober S. Donor-type CD4(+)CD25(+) regulatory T cells suppress lethal acute graft-versus-host disease after allogeneic bone marrow transplantation. J Exp Med. 2002;196(3):389-399.
30. Nguyen VH, Shashidhar S, Chang DS, et al. The impact of regulatory T cells on T-cell immunity following hematopoietic cell transplantation. Blood. 2008;111(2):945-953.

31. Di Ianni M, Falzetti F, Carotti A, et al. Tregs prevent GVHD and promote immune reconstitution in HLA-haploidentical transplantation. Blood. 2011;117(14):3921-3928.
32. Martelli MF, Di Ianni M, Ruggeri L, et al. HLA-haploidentical transplantation with regulatory and conventional T-cell adoptive immunotherapy prevents acute leukemia relapse. Blood. 2014;124(4):638-644.
33. Ciceri F, Bonini C, Stanghellini MT, et al. Infusion of suicide-gene-engineered donor lymphocytes after family haploidentical haemopoietic stem-cell transplantation for leukaemia (the TK007 trial): a non-randomised phase I-II study. Lancet Oncol. 2009;10(5):489-500.
34. Berenbaum MC, Brown IN. Prolongation of homograft survival in mice with single doses of cyclophosphamide. Nature. 1963;200:84.
35. Berenbaum MC, Brown IN. Dose-response relationships for agents inhibiting the immune response. Immunology. 1964;7:65-71.
36. Santos GW, Owens AH. Production of graft-versus-host disease in the rat and its treatment with cytotoxic agents. Nature. 1966;210(5032):139-140.
37. Mayumi H, Himeno K, Shin T, Nomoto K. Drug-induced tolerance to allografts in mice. VI. Tolerance induction in H-2-haplotype-identical strain combinations in mice. Transplantation. 1985;40(2):188-194.
38. Luznik L, Jalla S, Engstrom LW, Iannone R, Fuchs EJ. Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide. Blood. 2001;98(12):3456-3464.
39. Luznik L, Engstrom LW, Iannone R, Fuchs EJ. Posttransplantation cyclophosphamide facilitates engraftment of major histocompatibility complex-identical allogeneic marrow in mice conditioned with low-dose total body irradiation. Biol Blood Marrow Transplant. 2002;8(3):131-138.
40. Kanakry CG, Ganguly S, Zahurak M, et al. Aldehyde dehydrogenase expression drives human regulatory T cell resistance to post-transplantation cyclophosphamide. Sci Transl Med. 2013;5(211):211ra157.
41. Kastan MB, Schlaffer E, Russo JE, Colvin OM, Civin CI, Hilton J. Direct demonstration of elevated aldehyde dehydrogenase in human hematopoietic progenitor cells. Blood. 1990;75(10):1947-1950.
42. Jones RJ, Barber JP, Vala MS, et al. Assessment of aldehyde dehydrogenase in viable cells. Blood. 1995;85(10):2742-2746.
43. O'Donnell PV, Luznik L, Jones RJ, et al. Nonmyeloablative bone marrow transplantation from partially HLA-mismatched related donors using posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2002;8(7):377-386.
44. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2008;14(6):641-650.
45. Munchel A, Kesserwan C, Symons HJ, et al. Nonmyeloablative, HLA-haploidentical bone marrow transplantation with high dose, post-transplantation cyclophosphamide. Pediatr Rep. 2011;3 Suppl 2:e15.
46. Ciurea SO, Mulanovich V, Saliba RM, et al. Improved early outcomes using a T cell replete graft compared with T cell depleted haploidentical hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2012;18(12):1835-1844.
47. Devillier R, Bramanti S, Furst S, et al. T-replete haploidentical allogeneic transplantation using post-transplantation cyclophosphamide in advanced AML and myelodysplastic syndromes. Bone Marrow Transplant. 2016;51(2):194-198.
48. Ciurea SO, Zhang MJ, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. Blood. 2015;126(8):1033-1040.
49. Bashey A, Zhang X, Sizemore CA, et al. T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. J Clin Oncol. 2013;31(10):1310-1316.
50. Bashey A, Zhang X, Jackson K, et al. Comparison of outcomes of hematopoietic cell transplants from T-replete haploidentical donors using post-transplantation cyclophosphamide with 10 of 10 HLA-A, -B, -C, -DRB1, and -DQB1 allele-matched unrelated donors and HLA-identical sibling donors: a multivariable analysis including disease risk index. Biol Blood Marrow Transplant. 2016;22(1):125-133.
51. Di Stasi A, Milton DR, Poon LM, et al. Similar transplantation outcomes for acute myeloid leukemia and myelodysplastic syndrome patients with haploidentical versus 10/10 human leukocyte antigen-matched unrelated and related donors. Biol Blood Marrow Transplant. 2014;20(12):1975-1981.
52. Rashidi A, DiPersio JF, Westervelt P, et al. Comparison of outcomes after peripheral blood haploidentical versus matched unrelated donor allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia: a retrospective single-center review. Biol Blood Marrow Transplant. 2016;22(9):1696-1701.
53. How J, Slade M, Vu K, et al. T Cell-Replete T cell-replete peripheral blood haploidentical hematopoietic cell transplantation with post-transplantation cyclophosphamide results in outcomes similar to transplantation from traditionally matched donors in active disease acute myeloid leukemia. Biol Blood Marrow Transplant. 2017;23(4):648-653.
54. Piemontese S, Ciceri F, Labopin M, et al. A comparison between allogeneic stem cell transplantation from unmanipulated haploidentical and unrelated donors in acute leukemia. J Hematol Oncol. 2017;10(1):24.
55. Rashidi A, Slade M, DiPersio JF, Westervelt P, Vij R, Romee R. Post-transplant high-dose cyclophosphamide after HLA-matched vs haploidentical hematopoietic cell transplantation for AML. Bone Marrow Transplant. 2016;51(12):1561-1564.
56. Salvatore D, Labopin M, Ruggeri A, et al. Outcomes of non T cell-depleted haploidentical HSCT versus HSCT from matched sibling donors in patients with acute myeloid leukemia in first complete remission, an ALWP-EBMT study. 22nd European Hematology Association Congress; 2017; Madrid, Spain; 2017.
57. Versluis J, Labopin M, Ruggeri A, et al. Alternative donors for allogeneic hematopoietic stem cell transplantation in poor-risk AML in CR1. Blood Advances. 2017;1:477-485.
58. Armand P, Gibson CJ, Cutler C, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. Blood. 2012;120(4):905-913.
59. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood. 2014;123(23):3664-3671.
60. McCurdy SR, Kanakry JA, Showel MM, et al. Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide. Blood. 2015;125(19):3024-3031.
61. Tischer J, Engel N, Fritsch S, et al. Second haematopoietic SCT using HLA-haploidentical donors in patients with relapse of acute leukaemia after a first allogeneic transplantation. Bone Marrow Transplant. 2014;49(7):895-901.
62. Ringden O, Labopin M, Ciceri F, et al. Is there a stronger graft-versus-leukemia effect using HLA-haploidentical donors compared with HLA-identical siblings? Leukemia. 2016;30(2):447-455.
63. Ballen KK, Spitzer TR, Yeap BY, et al. Double unrelated reduced-intensity umbilical cord blood transplantation in adults. Biol Blood Marrow Transplant. 2007;13(1):82-89.
64. Brunstein CG, Barker JN, Weisdorf DJ, et al. Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplantation outcomes in 110 adults with hematologic disease. Blood. 2007;110(8):3064-3070.
65. Brunstein CG, Fuchs EJ, Carter SL, et al. Alternative donor transplantation after reduced intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. Blood. 2011;118(2):282-288.
66. Laughlin MJ, Barker J, Bambach B, et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. N Engl J Med. 2001;344(24):1815-1822.
67. Barker JN, Weisdorf DJ, DeFor TE, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. Blood. 2005;105(3):1343-1347.
68. Eapen M, Rocha V, Sanz G, et al. Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis. Lancet Oncol. 2010;11(7):653-660.
69. Rocha V, Aversa F, Labopin M, et al. Outcomes of unrelated cord blood and haploidentical stem cell transplantation in adults with acute leukaemia. Blood. 2005;106(11):301.
70. Raiola AM, Dominietto A, di Grazia C, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. Biol Blood Marrow Transplant. 2014;20(10):1573-1579.
71. Ruggeri A, Labopin M, Sanz G, et al. Comparison of outcomes after unrelated cord blood and unmanipulated haploidentical stem cell transplantation in adults with acute leukemia. Leukemia. 2015;29(9):1891-1900.
72. El-Cheikh J, Crocchiolo R, Furst S, et al. Unrelated cord blood compared with haploidentical grafts in patients with hematological malignancies. Cancer. 2015;121(11):1809-1816.
73. Giralt S, Logan B, Rizzo D, et al. Reduced-intensity conditioning for unrelated donor progenitor cell transplantation: long-term follow-up of the first 285 reported to the national marrow donor program. Biol Blood

Marrow Transplant. 2007;13(7):844-852.
74. Huang XJ, Liu DH, Liu KY, et al. Haploidentical hematopoietic stem cell transplantation without in vitro T-cell depletion for the treatment of hematological malignancies. Bone Marrow Transplant. 2006;38(4):291-297.
75. Huang XJ, Liu DH, Liu KY, et al. Treatment of acute leukemia with unmanipulated HLA-mismatched/haploidentical blood and bone marrow transplantation. Biol Blood Marrow Transplant. 2009;15(2):257-265.
76. Wang Y, Liu DH, Liu KY, et al. Long-term follow-up of haploidentical hematopoietic stem cell transplantation without in vitro T cell depletion for the treatment of leukemia: nine years of experience at a single center. Cancer. 2013;119(5):978-985.
77. Luo Y, Xiao H, Lai X, et al. T-cell-replete haploidentical HSCT with low-dose anti-T-lymphocyte globulin compared with matched sibling HSCT and unrelated HSCT. Blood. 2014;124(17):2735-2743.
78. Wang Y, Liu DH, Xu LP, et al. Superior graft-versus-leukemia effect associated with transplantation of haploidentical compared with HLA-identical sibling donor grafts for high-risk acute leukemia: an historic comparison. Biol Blood Marrow Transplant. 2011;17(6):821-830.
79. Chen XH, Gao L, Zhang X, et al. HLA-haploidentical blood and bone marrow transplantation with anti-thymocyte globulin: long-term comparison with HLA-identical sibling transplantation. Blood Cells Mol Dis. 2009;43(1):98-104.
80. Lu DP, Dong L, Wu T, et al. Conditioning including antithymocyte globulin followed by unmanipulated HLA-mismatched/haploidentical blood and marrow transplantation can achieve comparable outcomes with HLA-identical sibling transplantation. Blood. 2006;107(8):3065-3073.
81. Wang Y, Liu QF, Xu LP, et al. Haploidentical vs identical-sibling transplant for AML in remission: a multicenter, prospective study. Blood. 2015;125(25):3956-3962.
82. Sun Y, Beohou E, Labopin M, et al. Unmanipulated haploidentical versus matched unrelated donor allogeneic stem cell transplantation in adult patients with acute myelogenous leukemia in first remission: a retrospective pair-matched comparative study of the Beijing approach with the EBMT database. Haematologica. 2016;101(8):e352-354.
83. Ruggeri A, Sun Y, Labopin M, et al. Post-transplant cyclophosphamide versus anti-thymocyte globulin as graft- versus-host disease prophylaxis in haploidentical transplant. Haematologica. 2017;102(2):401-410.
84. Raiola AM, Dominietto A, Ghiso A, et al. Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. Biol Blood Marrow Transplant. 2013;19(1):117-122.
85. Bacigalupo A, Dominietto A, Ghiso A, et al. Unmanipulated haploidentical bone marrow transplantation and post-transplant cyclophosphamide for hematologic malignanices following a myeloablative conditioning: an update. Bone Marrow Transplant. 2015;50 Suppl 2:S37-39.
86. Solomon SR, Sizemore CA, Sanacore M, et al. Haploidentical transplantation using T cell replete peripheral blood stem cells and myeloablative conditioning in patients with high-risk hematologic malignancies who lack conventional donors is well tolerated and produces excellent relapse-free survival: results of a prospective phase II trial. Biol Blood Marrow Transplant. 2012;18(12):1859-1866.
87. Solomon SR, Sizemore CA, Sanacore M, et al. Total body irradiation-based myeloablative haploidentical stem cell transplantation is a safe and effective alternative to unrelated donor transplantation in patients without matched sibling donors. Biol Blood Marrow Transplant. 2015;21(7):1299-1307.
88. Rubio MT, Savani BN, Labopin M, et al. Impact of conditioning intensity in T-replete haplo-identical stem cell transplantation for acute leukemia: a report from the acute leukemia working party of the EBMT. J Hematol Oncol. 2016;9:25.
89. Ruggeri A, Labopin M, Bacigalupo A, Gulbas Z, Koc Y, D B. Use of bone marrow or peripheral blood stem cell grafts in non T cell depleted haploidentical transplants using post-transplant cyclophosphamide, an ALWP-EBMT analysis. 58th American Society of Hematology; 2016; San Diego, CA; 2016.
90. Peccatori J, Forcina A, Clerici D, et al. Sirolimus-based graft-versus-host disease prophylaxis promotes the in vivo expansion of regulatory T cells and permits peripheral blood stem cell transplantation from haploidentical donors. Leukemia. 2015;29(2):396-405.
91. Cieri N, Greco R, Crucitti L, et al. Post-transplantation cyclophosphamide and sirolimus after conditioning and peripheral blood stem cells. Biol Blood Marrow Transplant. 2015;21(8):1506-1514.
92. Castagna L, Crocchiolo R, Furst S, et al. Bone marrow compared with peripheral blood stem cells for haploidentical transplantation with a nonmyeloablative conditioning regimen and post-transplantation cyclophosphamide. Biol Blood Marrow Transplant. 2014;20(5):724-729.
93. O'Donnell PV, Eapen M, Horowitz MM, et al. Comparable outcomes with marrow or peripheral blood as stem cell sources for hematopoietic cell transplantation from haploidentical donors after non-ablative conditioning: a matched-pair analysis. Bone Marrow Transplant. 2016;51(12):1599-1601.
94. Kasamon YL, Bolanos-Meade J, Prince GT, et al. Outcomes of nonmyeloablative HLA-haploidentical blood or marrow transplantation with high-dose post-transplantation cyclophosphamide in older adults. J Clin Oncol. 2015;33(28):3152-3161.
95. Blaise D, Furst S, Crocchiolo R, et al. Haploidentical T cell-replete transplantation with post-transplantation cyclophosphamide for patients in or above the sixth decade of age compared with allogeneic hematopoietic stem cell transplantation from a human leukocyte antigen-matched related or unrelated donor. Biol Blood Marrow Transplant. 2016;22(1):119-124.
96. Canaani J, Savani BN, Labopin M, et al. Impact of ABO incompatibility on patients' outcome after haploidentical hematopoietic stem cell transplantation for acute myeloid leukemia - a report from the Acute Leukemia Working Party of the EBMT. Haematologica. 2017;102(6):1066-1074.
97. Walter RB, Gooley TA, Wood BL, et al. Impact of pretransplantation minimal residual disease, as detected by multiparametric flow cytometry, on outcome of myeloablative hematopoietic cell transplantation for acute myeloid leukemia. J Clin Oncol. 2011;29(9):1190-1197.
98. Walter RB, Buckley SA, Pagel JM, et al. Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission. Blood. 2013;122(10):1813-1821.
99. Ivey A, Hills RK, Simpson MA, et al. Assessment of minimal residual disease in standard-risk AML. N Engl J Med. 2016;374(5):422-433.
100. Anthias C, Dignan FL, Morilla R, et al. Pre-transplant MRD predicts outcome following reduced-intensity and myeloablative allogeneic hemopoietic SCT in AML. Bone Marrow Transplant. 2014;49(5):679-683.
101. Buccisano F, Maurillo L, Piciocchi A et al. Variable outcome of allogeneic stem cell transplant according to the different levels of pre-transplant minimal residual disease, in adult patients with acute myeloid leukemia. Blood. 2015;126(23):3230.
102. Wang Y, Liu DH, Liu KY, et al. Impact of pre-transplantation risk factors on post transplantation outcome of patients with acute myeloid leukemia in remission after haploidentical hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2013;19(2):283-290.
103. Zhao XS, Qin YZ, Liu YR, et al. The impact of minimal residual disease prior to unmanipulated haploidentical hematopoietic stem cell transplantation in patients with acute myeloid leukemia in complete remission. Leuk Lymphoma. 2017;58(5):1135-1143.
104. Bachegowda LS, Saliba RM, Ramlal R, et al. Predictive model for survival in patients with AML/MDS receiving haploidentical stem cell transplantation. Blood. 2017;129(22):3031-3033.
105. Apperley J, Niederwieser D, Huang XJ, et al. Haploidentical hematopoietic stem cell transplantation: a global overview comparing Asia, the European Union, and the United States. Biol Blood Marrow Transplant. 2016;22(1):23-26.
106. Aversa F, Prezioso L, Manfra I, Galaverna F, Spolzino A, Monti A. Immunity to infections after haploidentical hematopoietic stem cell transplantation. Mediterr J Hematol Infect Dis. 2016;8(1):e2016057.
107. Lin CJ, Vader JM, Slade M, DiPersio JF, Westervelt P, Romee R. Cardiomyopathy in patients after posttransplant cyclophosphamide-based hematopoietic cell transplantation. Cancer. 2017;123(10):1800-1809.
108. Majzner RG, Mogri H, Varadhan R, et al. Post-transplantation cyclophosphamide after bone marrow transplantation is not associated with an increased risk of donor-derived malignancy. Biol Blood Marrow Transplant. 2017;23(4):612-617.
109. Chang YJ, Luznik L, Fuchs EJ, Huang XJ. How do we choose the best donor for T-cell-replete, HLA-haploidentical transplantation? J Hematol Oncol. 2016;9:35.
110. Gorin NC, Labopin M, Piemontese S, et al. T-cell-replete haploidentical transplantation versus autologous stem cell transplantation in adult acute leukemia: a matched pair analysis. Haematologica. 2015;100(4): 558-564.
111. Kanakry CG, Fuchs EJ, Luznik L. Modern approaches to HLA-haploidentical blood or marrow transplantation. Nat Rev Clin Oncol. 2016;13(1):10-24.