Front. Med. 2019, 13(1): 45–56
https://doi.org/10.1007/s11684-017-0595-7

REVIEW

Everyone has a donor: contribution of the Chinese experience to global practice of haploidentical hematopoietic stem cell transplantation

Meng Lv[1], Yingjun Chang[1], Xiaojun Huang (✉)[1,2]

[1]*Peking University People's Hospital, Peking University Institute of Hematology, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing 100044, China;* [2]*Peking-Tsinghua Center for Life Sciences, Beijing 100044, China*

Abstract **Human leukocyte antigen (HLA)-matched donors for hematopoietic stem cell transplantation (HSCT) have long been scarce in China. Haploidentical (haplo) donors are available for the vast majority of patients, but toxicity has limited this approach. Three new approaches for haplo-HSCT originated from Italy, China, and USA in 1990 and have been developed to world-renowned system up to now. The Chinese approach have been greatly improved by implementing new individualized conditioning regimens, donor selection based on non-HLA systems, risk-directed strategies for graft-versus-host disease and relapse, and infection management. Haplo-HSCT has exhibited similar efficacy to HLA-matched HSCT and has gradually become the predominant donor source and the first alternative donor choice for allo-HSCT in China. Registry-based analyses and multicenter studies adhering to international standards facilitated the transformation of the unique Chinese experience into an inspiration for the refinement of global practice. This review will focus on how the new era in which "everyone has a donor" will become a reality in China.**

Keywords haploidentical hematopoietic stem cell transplantation; conditioning; graft-versus-host disease; relapse; infection; donor selection

Introduction

Hematopoietic stem cell transplantation (HSCT) is the most powerful curative therapy for the majority of hematological malignancies. However, human leukocyte antigen (HLA)-matched HSCT donors have long been scarce in China due to a deficiency of HLA-identical siblings and a relatively small unrelated donor (URD) program [1,2]. Haploidentical (haplo) family donors, such as parents or children, offer the benefits of rapid and nearly universal donor availability. However, the HLA barrier of haplo-HSCT has been formidable until recent decades due to the high incidence of rejection and severe graft-versus-host disease (GvHD) [3–5]. The three main approaches for haplo-HSCT in the world are as follows [6–8]: (1) T cell depletion (TCD)-based regimens, which originated from the Perugia group, Italy [9–11]; (2) granulocyte colony-stimulating factor (G-CSF) plus anti-thymocyte globulin (ATG)-based regimens with unmanipulated T cell replete graft, which originated from the Peking group, China [12,13]; and (3) post-transplantation cyclophosphamide (PT-CY)-based regimens with unmanipulated T cell replete graft, which originated from the Baltimore group, USA [14,15]. The historical aspects of these approaches had been previously reviewed [7]. The present review will focus on the progress of the Chinese experience with haplo-HSCT and its potential global contributions.

Received April 14, 2017; accepted September 30, 2017
Correspondence: Xiaojun Huang, huangxiaojun@bjmu.edu.cn

Unmanipulated haplo-HSCT with G-CSF and ATG

New approaches to haplo-HSCT have been continually pursued over the past two decades. The Western world first introduced *in vitro* TCD in the 1990s. However, this method required expensive laboratory facilities with significant expertise in cell manipulation. Furthermore, this technique was associated with poor T cell function and thus high incidence of mortality because of infections and

relapse rates [7,9–11]. Since the 2000s, two haplo-HSCT regimens using unmanipulated T cell replete grafts were developed in China and USA; these regimens have now become popular approaches [8].

In a series of pilot studies on G-CSF-induced immune tolerance by Huang's group, bone marrow T cell hyporesponsiveness could be induced by the upregulation of monocytes and plasmacytoid dendritic cells (DC2) and the downregulation of co-stimulatory signals during *in vivo* G-CSF administration. The polarization of T cells from Th1 to Th2 could be maintained after *in vitro* mixture of G-CSF-mobilized peripheral blood grafts (G-PB) and G-CSF primed bone marrow grafts (G-BM) [16,17]. Combinations of G-CSF and ATG were proposed to play a fundamental role in overcoming HLA barriers [18] through the action of regulatory B cell, regulatory T cell, Th17/Tc 17, and myeloid-derived suppressor cells [19–25].

Based on the mechanistic research on cytokine-induced immune tolerance, in 2000 Huang and colleagues at Peking University initiated a pilot study investigating unmanipulated haplo-HSCT without *in vitro* TCD for the treatment of acute leukemia. The study mainly included mixed grafts of G-PB and G-BM, modified busulfan/cyclophosphamide (Bu/Cy) plus ATG for myeloablative conditioning, and cyclosporine A + methotrexate + mycophenolate mofetil for intensified GvHD prophylaxis. All patients ($n = 58$) in the pilot cohort achieved sustained, full donor-type engraftment with an acceptable incidence of grades II–IV acute GvHD (aGvHD, 37.9%) and chronic GvHD (cGvHD, 65.4%). The 2-year disease-free survival (DFS) rates for standard- and high-risk patients were 77.6% and 63.2%, respectively [26,27]. The cohort was updated [13,28–30] and expanded to 756 cases in 2010, with 99.5% sustained myeloid engraftment, 43% grades II–IV aGvHD, and 53% cGvHD. The three-year DFS for standard- and high-risk patients was 68% and 49%, respectively [31]. During the same period, haplo-HSCT following ATG + G-CSF experience was also developed by the airforce group [32,33].

These promising results justified studies on the feasibility of unmanipulated haplo-HSCT with G-CSF and ATG for leukemia. During the last 10 years, several key techniques have been improved by clinical studies from various centers (Table 1), including new conditioning regimens and improved management of complications, such as GvHD, relapse, and infection.

Individualized protocols expand the target patient population

ATG is a critical component of the conditioning of T cell replete haplo-HSCT, but its optimal dose remains unknown. In a prospective, randomized trial, the Peking group revealed that 10 mg/kg thymoglobulin (rabbit ATG by Genzyme) reduced grades III and IV severe aGVHD (4.5% vs.16.1%) and moderate-to-severe cGVHD (30.4% vs. 56.3%) compared with 6 mg/kg, with comparable five-year DFS (75.6% vs. 69.6%, $P = 0.283$) and improved the 5-year probability of GVHD relapse-free survival (41.0% vs. 26.8%) [34,35]. Another haplo-HSCT regimen, which utilized low-dose ATG-F (10 mg/kg rabbit ATG by Fresenius, standard 30–60 mg/kg), introduced by the Zhejiang group also achieved acceptable incidences of severe aGvHD (17.2%) and cGVHD (41.4%) [36].

In addition to standard Bu/Cy conditioning, a new regimen introduced by the Peking group, which included TBI (700 cGy)/Cy (3.6 g/m^2) plus ATG, was also proven to be feasible for the treatment of unmanipulated haplo-HSCT. Compared with the Bu/Cy regimen, TBI/Cy plus ATG exhibited stable engraftment and a low incidence of liver toxicity (10.5% vs. 37.7%) and hemorrhagic cystitis (23.7% vs. 49.3%) for treating acute lymphoblastic leukemia and provided comparable results to sibling donors in high-risk acute leukemia [37].

For patients with refractory leukemia, intensified conditioning introduced by the Nanfang group may reduce the high leukemia cell burden and improve outcomes. Using a combination of Flu, cytarabine, TBI, Cy, and etoposide for conditioning in the haplo-setting, Liu *et al*. showed that intensified conditioning decreases the five-year relapse rate from 33.9% to 27.3% and might be a good approach for refractory leukemia, as well as acute leukemia of ambiguous lineage [38–40]. IDA-intensified haplo-HSCT introduced by the Wuhan Union group improved the dismal prognosis of pre-transplant MRD, yielding 3-year DFS of 47.3% [41].

Selected older patients (age > 50) with low HCT-CI ($\leqslant 2$) and good performance status could tolerate myeloablative haplo-HSCT with similar outcomes compared with younger adults [42]. For patients above 60 years of age, haplo-HSCT with a reduced intensity regimen by substitution of cyclophosphamide with Flu was proven to be feasible with similar engraftment and relapse rates to myeloablative conditioning [43]. Utilizing induction chemotherapy with the infusion of HLA-mismatched G-PB, Ai *et al.* from the military medical sciences group showed the superiority of "microtransplantation" over chemotherapy for elderly patients suffering from AML (two-year DFS 38.9% vs. 10.0%) [44]. Further multicenter studies will be needed to compare standard induction followed by microtransplantation with traditional HLA-matched HSCT or haplo-HSCT.

Compared with the mixed grafts of G-PB and G-BM in haplo-HSCT introduced by the Beijing group, the modified G-CSF + ATG protocols with pure G-BM or G-PB were also feasible as proven by various centers. A propensity score method-based multicenter study demonstrated that haplo-HSCT with mixed grafts achieved better 3-year-DFS compared with G-PB alone (59.9% vs. 44.3%) [45]. Most

Table 1 G-CSF + ATG-based haplo-HSCT for leukemia

Center Nation	Patients *n*	Conditioning	Donor Grafts	aGvHD II–IV/III and IV	cGvHD Total/Ex	Relapse	TRM	OS/DFS	Publication/ References
Wuhan Union China	110	Bu + Cy + IDA ATG (T 6 mg) + CD25	G-PB± G-BM	II–IV 28.6% III and IV 14.3%	33.2% Ex 13.8%	23.4%	18.8%	Three-year OS 62.9% DFS 59.1	Bone Marrow Transplant 2017 [41]
PLA General China	130	Bu + Cy or TBI ATG (T 10 mg)	G-PB	II–IV 26.9% III and IV 14.9%	38.6% Ex 16.5%	26.9%	24.1%	Three-year OS 45.6% DFS 44.2%	Bone Marrow Transplant 2016 [53]
Zhujiang China	105	Bu + Cy + Flu ATG (T 12.5 mg)	G-PB	II–IV 21.9% III and IV 14.3%	24.1% Ex 3.8%	21.0%	34.9%	Three-year OS 52.6% DFS 43.1%	Bone Marrow Transplant 2016 [54]
Fujian Union China	63	Bu + Cy + Flu ATG (T 10 mg/F 40 mg)	G-BM + G-PB	II–IV 11.0% III and IV 6.3%	9.5%	11.9%	20.6%	Two-year OS 61.3% DFS 58.3%	Oncotarget 2016 [55]
Milan/Berlin Italy/Germany	121	Treosulfan + Flu ATG (F 10 mg)	G-PB	II–IV 35% III and IV 22%	35.5% Ex 24.8%	36%	31%	Three-year OS 25% DFS 20%	Leukemia 2015 [52]
Catholic South Korea	80	Bu + TBI + Flu ATG (T 6 mg)	G-PB	II–IV 47.5% III and IV 11.2%	45.0% Ex 26.3%	18.8%	12.5%	Two-year OS 66.0% DFS 61.1%	Biol Blood Marrow Transplant 2015 [51]
Tokyo, Japan	34	Bu + Flu ATG (F 8 mg)	G-PB	II–IV 30.7%	Ex 20%	41.2%	26.5%	One-year OS 47.1%	Biol Blood Marrow Transplant 2015 [50]
Peking China	1210	Bu + Cy ATG (T 10 mg)	G-BM + G-PB	II–IV 40% III and IV 12%	50% Ex 21%	17.0%	17.0%	Three-year OS 70% DFS 67%	Blood 2014 [66]
Zhejiang China	99	Bu + Cy ATG (F 10 mg)	G-PB	II–IV 42.4% III and IV 17.2%	41.4%	14.2%	23.2%	Five-year OS 60.8% DFS 58.3%	Blood 2014 [36]
Xinqiao, etc. Seven centers China	178	Bu + Cy + ATG	G-BM + G-PB	II–IV 42.4% III and IV 10.2%	52.8%	38.2%	6.7%	Two-year OS 59.6% DFS 55.1%	Biol Blood Marrow Transplant 2014 [49]
Soochow China	50	Bu + Cy or TBI ATG (T 10 mg)	G-BM±G-PB + Cord	II–IV 20% III and IV 10%	19.3%	19.8%	16.2%	One-year OS 78.6% DFS 64.0%	Bone Marrow Transplant 2014 [48]
Pescara/Hashomer, Italy/Israel	80	Bu + Flu ATG (F 20 mg) + CD25	G-BM	II–IV 24% III and IV 5%	12% Ex 5%	28%	36%	Three-year OS 45% DFS 38%	Blood 2013 [47]
Asan, etc. South Korea	83	Bu + Flu ATG (T 12 mg)	G-PB	II–IV 20%	34% Ex 18%	32.5%	18%	Two-year OS 56% DFS 45%	Blood 2011 [46]

Abbreviation: Bu, busulfan; Cy, cyclophosphamide; TBI, total body irradiation; ATG, anti-human thymocyte globulin; T, thymoglobulin; F, ATG-F; Flu, fludarabine; IDA, idarubicin; CD25, basiliximab; OS, overall survival; DFS, disease-free survival; TRM, treatment-related mortality; "±", plus or not; "+", plus; Ex, extensive.

unmanipulated haplo-HSCTs with G-CSF and ATG for leukemia are summarized in Table 1 [46–55].

Haplo-HSCT has been considered only as a third-line option for patients with severe aplastic anemia (SAA) in the absence of HLA identical sibling donor (ISD) or URD, with a 25% probability of graft failure and five-year OS of less than 30% [56,57]. However, a new regimen, including Bu/Cy and ATG combined with unmanipulated grafts, led to the increasing usage of haplo-HSCT in SAA. According to Xu *et al*., all patients ($n = 19$) in the pilot cohort achieved 100% donor myeloid engraftment, with a 5-year OS of 68.4% [58]. In a later multicenter study that compared haplo-HSCT and ISD HSCT as salvage treatments for SAA, the rates of grades II–IV aGvHD (33.7% vs. 4.2%) and one-year cGvHD (22.4% vs. 6.6%) were still high in the haplo setting. However, the 3-year OS (89.0% vs. 91.0%), failure-free survival (86.8% vs. 80.3%), and grades III and IV aGvHD (7.9% vs. 2.1%) were similar among the groups [59]. In a later registry-based analysis of SAA patients without previous failure of immunosuppressive therapy, haplo-HSCT achieved similar results to ISD HSCT as early treatment. Aside from the G-CSF plus ATG-based regimen, the People's Liberation Army General Hospital introduced a PT-CY regimen in 20 SAA patients, which was associated with 85% engraftment in first transplant and 85% failure-free survival in short follow-up (median 17 months). The efficacy needs to be confirmed using increased sample size and long-term follow-up [60]. Based on these promising experiences, haplo-HSCT has been promoted to a second-line therapy in the aplastic anemia guidelines of Asia-Pacific Hematology Consortium [61] and the British guidelines [62].

Donor selection based on a non-HLA system improves outcomes in haplo-HSCT

HLA match plays a predominant role in the selection of the best donor among unrelated transplants but does not influence the outcomes in haplo-HSCT [63,64]. A given patient might have multiple choices for a haplo donor, raising the question, "who is the best haplo donor?"

Donor-specific anti-HLA antibodies (DSAs) are associated with primary graft failure and treatment mortality (TRM). Chang *et al*. reported that DSAs (MFI $\geqslant$ 10 000) were correlated with primary graft rejection and were associated with poor primary graft function (MFI $\geqslant$ 2000). This finding supported the rationale for screening DSAs before haplo-HSCT for donor selection [65].

Basing on a large sample size and relative consistency of transplant variables, young male NIMA-mismatched donors were suggested to reduce the risk of severe GvHD or relapse. As recommended, transplants from older mothers and NIPA-mismatched donors should probably be avoided [66]. $CD4^+CD25^+CD45RA^+$ Treg was reported to contribute to low aGvHD in NIMA-mismatched haplo-HSCT. Additionally, other non-HLA systems, such as donor inhibitory killer cell immunoglobulin-like receptors (KIRs), might also facilitate donor selection in haplo-HSCT. Currently, an algorithm based on unmanipulated haplo-HSCT was proposed for donor selection; however, the mechanisms remain to be further elucidated [67].

Risk-adapted intervention to reduce GvHD post-haplo-HSCT

As mentioned above, although rates of grades III and IV aGvHD and extensive cGvHD were comparable between haplo-HSCT and ISD HSCT, total GvHD remained a common problem with high rates observed in haplo-HSCT. As reported in a follow-up of the largest haplo-HSCT cohort, the incidence of grades II–IV aGvHD was 43%, and the two-year cumulative incidence of total cGvHD was 53% [31]. Meanwhile, rates of grades II–IV aGvHD and cGvHD were generally below 10%–20% in MSD-HSCT [68–70].

In a series of studies of biomarkers for GvHD, CD4/CD8 ratios in G-BM allograft $\geqslant$ 1.16, $CD56^{bright}$ NK cells in allograft $> 1.9 \times 10^6$/kg, M-MDSC in allograft $< 1.22 \times 10^7$/kg, and other components of grafts provided predictive markers for the onset of aGvHD after haplo-HSCT [23,71,72]. However, whether these biomarkers would be useful for guiding interventions remained unknown. Chang *et al*. reported that a cohort of patients ($n = 228$) can be stratified into high-risk and low-risk arms according to CD4/CD8 ratios in allografts. Patients in the high-risk arms (CD4/CD8 $\geqslant$ 1.16) were randomly assigned at a 1:1 ratio to either the additional low-dose glucocorticoid prophylaxis group or the control group. The cumulative incidence of grades II–IV aGvHD on day 100 was reduced from 48.1% to 20.9% by prophylaxis in the high-risk group, a rate comparable to the low-risk group (25.5%), without an increased rate of infections or delayed immune recovery [73]. For the first time, intervention based on risk stratification with biomarkers was proven feasible for the management of GvHD. It also established a concrete example of how precision medicine could be incorporated into clinical practice.

Mesenchymal stem cells (MSCs) are multipotent stromal cells with immunomodulatory properties. They have demonstrated promising efficacy for treating steroid-resistant GvHD. Co-transplantation of MSCs and HSCs also reduces aGvHD and cGvHD rates in MSD-HSCT, albeit with a potentially higher likelihood of leukemia recurrence [74]. The mechanism and usage of MSC infusions for GvHD prophylaxis remain to be evaluated. In a new double-blind trial of haplo-HSCT reported by Zhang *et al*., patients without cGvHD at day 100 were

randomly selected to receive either umbilical cord-derived MSCs (MSC group: 3×10^7 cells/100 mL per month) or normal saline for more than 4 months after transplantation. The 2-year cumulative incidence of cGVHD was reduced in the MSC group compared with that in the control group (27.4% vs. 49.0%, respectively, $P = 0.021$) without increasing the risk of relapse [75]. This trial might provide hope for preventing cGvHD after haplo-HSCT following an ATG and G-CSF protocol. Further evaluation and adjustment of infusion doses and intervals according to biomarker-directed risk stratification would be desirable.

Prophylaxis, intervention, and treatment of relapse post-haplo-HSCT

Relapse remains the most devastating problem after HSCT, accounting for nearly half of deaths [76]. Recent biomarker advances have facilitated the prediction of relapse risk by dynamic monitoring of MRD, chimerism, and other factors before or after allo-HSCT. Pre- and post-transplant risk-stratification-directed strategies for intervention and treatment might benefit patients by triggering more potent graft-versus-tumor effects without increasing treatment-associated mortality.

Donor lymphocyte infusion (DLI) is one of the most effective strategies for patients with recurrent hematological malignancies after allo-HSCT. However, traditional DLI is more effective for CML than for acute leukemia and carries a relatively high incidence of GvHD. Huang *et al*. reported that an infusion of G-CSF-mobilized peripheral blood progenitor cells with a short course of immunosuppression (modified DLI, mDLI) reduces the risk of aGvHD while maintaining the GVL effects after MSD-HSCT and haplo-HSCT [77,78]. Chemotherapy followed by mDLI improved the clinical outcomes compared with chemotherapy alone (DFS 36% vs. 0%) [79]. In a recent trial, MRD and GvHD-guided multiple consolidation chemotherapy and mDLI were proven to prevent a second relapse in patients with acute leukemia relapse post-transplant (CIR 22% vs. 56%). Meanwhile, the cumulative incidences of grades II or higher aGvHD were not associated with chemotherapy or mDLI treatments [80].

Given its efficient anti-leukemia effects (GVL) and safety by reducing TRM, mDLI could be used for intervention or prophylaxis before hematological relapse. Recent clinical trials and reports regarding the use of MRD or chimerism for guiding pre-emptive intervention post-allo-HSCT have been informative and helpful. In a cohort of 814 patients receiving allo-HSCT, where 105 patients were MRD +, mDLI reduced CIR from 64.4% to 27.8%, with improved OS (28.1% vs. 58.3% previously). However, this result was not significantly different compared with the MRD − patients [81]. Interferon-α (IFN-α), a well-known antitumor agent for chronic myeloid leukemia, has sparked renewed interest in its use for AML [82]. Mo *et al*. demonstrated that for patients with an unsatisfactory response to MRD-directed mDLI, IFN-α might induce a graft-versus-leukemia effect to improve mDLI efficacy and clear MRD [83]. Later, among patients who were MRD +, IFN-α was found to be associated with cGvHD more compared with mDLI (90.9% vs. 62.9%, $P < 0.001$). While NRM and DFS were comparable, IFN-α could be more easily used in an outpatient department [84].

For advanced leukemia with a high risk of relapse, Huang *et al*. showed that prophylactic mDLI can reduce the relapse rate to 51.3% after haplo-HSCT [78]. Intensified conditioning followed by early immunosuppressant withdrawal and DLI could further reduce the relapse rate of refractory acute leukemia [40]. In a recent multicenter study, prophylactic DLI at 45–60 days after transplantation followed by MRD and GvHD-guided multiple DLI for patients with refractory/relapsed leukemia further reduced the cumulative relapse rate to 32.4% with improved LFS and OS (50.3% and 51.4%) [85].

Infection management reduces TRM

Invasive fungal disease (IFD) remains a significant threat post-HSCT, especially in the haplo setting. Sun *et al*. reported in a single-center analysis that the incidence of IFD after unmanipulated haplo-HSCT is significantly higher than that after MSD-HSCT (7.1% vs. 3.3%), as well as in multivariable analysis (HR = 2.648, 95% CI 1.111–6.310; $P = 0.028$). However, the response to antifungal therapy and IFD-attributable mortality were similar between the two types of transplantation. This finding was further validated in the first large-scale observational study of IFD in China, the China Assessment of Antifungal Therapy in Hematological Disease. The incidences of proven IFD following ISD, URD, and haplo-HSCT were 4.47%, 11.64%, and 12.73%, respectively. In total, 83.9% of patients received antifungal prophylaxis. Empirical, pre-emptive, and targeted antifungals were used in 82.3%, 13.6%, and 4.1% of cases, respectively [86]. This observational study provided abundant information for refining future anti-IFD strategies.

As prolonged severe neutropenia (> 14 days) was identified as an independent risk factor for IFD [86], strategies to address neutropenia are desirable for reducing IFD-associated mortality. In a phase IV trial from the Shanghai group, 206 patients were randomly assigned to receive once-daily subcutaneous GM-CSF, G-CSF, or a combination of both. The authors of the study found that IFD-related mortality was lower in groups that received GM-CSF or G-CSF + GM-CSF compared with those that received G-CSF (1.47%, 1.45%, and 11.59%, respectively; $P = 0.016$). Furthermore, prophylactic GM-CSF was associated with lower 100-day transplantation-related

mortality and lower 100-day cumulative mortality, which suggests that incorporation of GM-CSF with G-CSF may promote myeloid engraftment in the haplo setting.

Among post-HSCT viral infections, Epstein–Barr virus (EBV)-related post-transplantation lymphoproliferative disorder (PTLD) after haplo-HSCT can seriously impair patient survival. In a large cohort study, a low absolute count of CD8 T lymphocytes and immunoglobulin M at day 30 and cytomegalovirus DNAemia after HSCT were found to be significantly associated with a high risk of PTLD. Patients who received rituximab-based therapy had significantly better two-year OS (48.2% vs. 13.2%, P = 0.02). EBV-specific cytotoxic T lymphocyte levels and DLI following rituximab-based therapy were associated with improved outcome after PTLD (five-year OS, 68.9%–70%) [87].

Everyone has a donor with development of the haplo-HSCT system

Numerous advances in stem cell transplantation during the past 16 years have included unmanipulated haplo-HSCT and the integration of G-CSF and ATG into new conditioning regimens; management of complications including GvHD, relapse, and infection; and refinement of donor selection based on a non-HLA system (Table 1). As a result, patient outcomes following this unique protocol have steadily improved, bringing an end to the old era of transplantation plagued by donor shortages.

According to a prospective study by Huang *et al*., unmanipulated haplo-HSCT with G-CSF and ATG was proven superior to chemotherapy as a post-remission treatment for intermediate- or high-risk AML or ALL in CR1. The cumulative relapse incidence for haplo-HSCT was 12.0% vs. 57.8% for chemotherapy, and the four-year DFS for haplo-HSCT was 73.1% vs. 44.2% for chemotherapy. Additionally, in multicenter studies, Wang *et al*. reported that haplo-HSCT had outcomes comparable to MSD-HSCT for adults with intermediate- or high-risk AML in CR1. Similar results were achieved in Philadelphia-negative high-risk ALL in CR1, MDS, and primary or salvage treatment for SAA [62,68–70,88]. Haplo-HSCT may also improve outcomes for children compared with umbilical cord blood transplantation [89]. Accordingly, haplo-HSCT was adopted as the first-choice alternative donor to HLA-ISD. Based on these outcomes, this unique system was named the "Beijing Protocol." As Kodera *et al*. from the Worldwide Network for Blood and Marrow Transplantation (WBMT) commented, "The Beijing Protocol was shown to be a reliable treatment strategy for patients without a suitable HLA-matched donor" [8].

The "Beijing Protocol" was adopted in the majority of Chinese HSCT centers ($n > 90$), whereas transplants following PT-CY- or TCD-based protocols were utilized less than 1% in Chinese registries of HSCT. The number of haplo-HSCT cases increased to approximately 2500 per year, making it the largest source of allo-HSCT donors (37.6%–51.5%) in China since 2013 (Fig. 1). The "Beijing Protocol" was also reproduced successfully in Italy, Israel, Korea, and Japan [4,47,90]. By contrast, according to the global survey by WBMT, haplo-HSCT with PT-CY is mainly used in the USA and partially in Europe and Australia [8]. The European Society for Blood and Marrow Transplantation reported that G-CSF + ATG-based regimens comprise 43%–45% of haplo-HSCT compared with PTCy, which comprises 27%–57% of haplo-HSCT, in Europe [91–93]. The largest cohorts from three different approaches are summarized in Table 2 [66,94,95]. As R. Handgretinger commented, "more than half of the HLA haplotype mismatched transplantations performed worldwide will follow similar protocols (to the Beijing Protocol)"[96]. Correspondingly, haplo-HSCT has been a global phenomenon as the frequency of haplo-HSCT has grown steadily from 3% to 5% to more than 10% of allo-HSCT in Europe and USA [97]. The global contribution of the "Beijing Protocol" and PT-CY thus heralds a new era where "everyone has a donor."

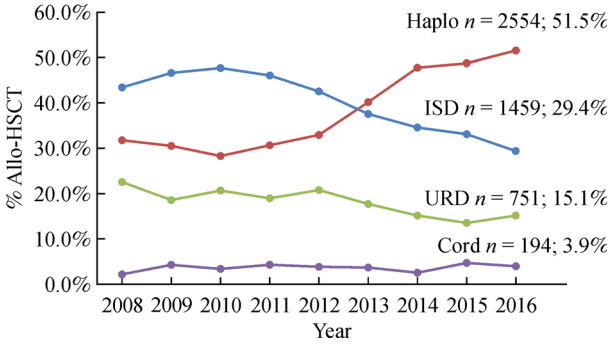

Fig. 1 Annual allo-HSCT cases of the Chinese Registry and percentage of different donor sources in 2008–2016. Haplo, haploidentical donors; ISD, HLA identical sibling donor; URD, unrelated donor; cord: cord blood.

Conclusions and perspectives

Substantial progress has been made in the field of haplo-HSCT in recent years in China. From a broader perspective, these innovative efforts from China may have contributed to the worldwide practice of HSCT.

However, several critical questions remain to be addressed. First, with the arrival of a new era where "everyone has a donor" [98], is there a shift from donor shortage to donor diversification? As most patients have many potential donors, including ISD and alternative

Table 2 Comparison of the largest cohort from different haplo-HSCT approaches for leukemia

	Beijing Protocol	Post-transplant cyclophosphamide	T cell depletion
Numbers of patients	1210	681	161
Graft failure	1%	9%–12%	3.7%
II–IV aGvHD	40%	25%–42%	12%
cGvHD	50%	20%–41%	3.7%
Relapse	17%	28%–45%	23%
TRM	17%	16%–17%	38.5%
DFS	Three-year 67%	Two-year 41%–54%	Four-year 38.5%
Reference	Blood 2014 [66]	J Clin Oncol 2017 [94]	Blood 2015 [95]

Abbreviation: aGvHD, acute graft-versus-host disease; cGvHD, chronic graft-versus-host disease; DFS, disease-free survival; TRM, treatment mortality.

donors, the question changes from "who's the best haplo donor?" to "who's the best alternative donor?" and, finally, to "who's the best donor?" Would an ISD donor always remain the first choice regardless of disease status or donor characteristics? Recent advances suggested that ABO incompatibility, age, and sex of donor–patient will have a major impact on outcomes instead of HLA compatibility [99]. How can we predict the outcomes of different donor sources under a uniform model? Addressing this question through large-scale registry-based studies, especially those involving the cooperation between China and the Western world, is of great importance. In addition, considering the rapid progression of immunotherapies, such as cellular therapy including CAR-T, CAR-NK, leukemia gene-specific CTL, and monoclonal antibodies such as PD-1/PD-L1, how can they be incorporated or bridged with allo-HSCT, especially in the largest pool of haplo-HSCT? Third, though T cell replete haplo-HSCT took place of TCD worldwide [100], trials of haplo-HSCT following partial depletion of αβ T and B cells continue to be explored [101]. Can we "design" the graft compositions for haplo-HSCT to improve outcomes following G-CSF + ATG or PT-CY regimens? Lastly, how can we further improve outcomes for elderly patients or those with comorbidities? Can we make treatment regimen decisions according to a patient's specific characteristics? All these questions would be critical matters to be addressed at a summit of international scholars.

With the development of international multicenter clinical trials and advances in translational research, the unique Chinese experience can continue to contribute to global practice for haplo-HSCT.

Acknowledgements

We would like to thank the American Journal Experts (https://www.aje.com) for providing editorial assistance. This work was supported by the National Natural Science Foundation of China (Nos. 81873445, 81470342, and 81670168), the Foundation for Innovative Research Groups of the National Natural Science Foundation of China (No. 81621001), and the Key Program of the National Natural Science Foundation of China (Nos. 81530046 and 81230013).

Compliance with ethics guidelines

Meng Lv, Yingjun Chang, and Xiaojun Huang declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by a relevant institutional review board or ethics committee.

References

1. Lv M, Huang XJ. Allogeneic hematopoietic stem cell transplantation in China: where we are and where to go. J Hematol Oncol 2012; 5(1): 10
2. Xu LP, Wu DP, Han MZ, Huang H, Liu QF, Liu DH, Sun ZM, Xia LH, Chen J, Wang HX, Wang C, Li CF, Lai YR, Wang JM, Zhou DB, Chen H, Song YP, Liu T, Liu KY, Huang XJ. A review of hematopoietic cell transplantation in China: data and trends during 2008–2016. Bone Marrow Transplant 2017; 52(11):1512–1518
3. Reisner Y, Hagin D, Martelli MF. Haploidentical hematopoietic transplantation: current status and future perspectives. Blood 2011; 118(23): 6006–6017
4. Velardi A. Haplo-BMT: which approach? Blood 2013; 121(5): 719–720
5. Szydlo R, Goldman JM, Klein JP, Gale RP, Ash RC, Bach FH, Bradley BA, Casper JT, Flomenberg N, Gajewski JL, Gluckman E, Henslee-Downey PJ, Hows JM, Jacobsen N, Kolb HJ, Lowenberg B, Masaoka T, Rowlings PA, Sondel PM, van Bekkum DW, van Rood JJ, Vowels MR, Zhang MJ, Horowitz MM. Results of allogeneic bone marrow transplants for leukemia using donors other than HLA-identical siblings. J Clin Oncol 1997; 15(5): 1767–1777
6. Fuchs EJ. Haploidentical transplantation for hematologic malignancies: where do we stand? Hematology Am Soc Hematol Educ Program 2012; 2012: 230–236
7. Kanakry CG, Fuchs EJ, Luznik L. Modern approaches to HLA-haploidentical blood or marrow transplantation. Nat Rev Clin Oncol 2016; 13(1): 10–24
8. Apperley J, Niederwieser D, Huang XJ, Nagler A, Fuchs E, Szer J, Kodera Y. 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
9. Aversa F, Tabilio A, Terenzi A, Velardi A, Falzetti F, Giannoni C, Iacucci R, Zei T, Martelli MP, Gambelunghe C, *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
10. Aversa F, Tabilio A, Velardi A, Cunningham I, Terenzi A, Falzetti F, Ruggeri L, Barbabietola G, Aristei C, Latini P, Reisner Y, Martelli MF, Felicini R, Falcinelli F, Carotti A, Perruccio K, Ballanti S, Santucci A, Gambelunghe C. 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
11. Aversa F, Terenzi A, Tabilio A, Falzetti F, Carotti A, Ballanti S, Felicini R, Falcinelli F, Velardi A, Ruggeri L, Aloisi T, Saab JP, Santucci A, Perruccio K, Martelli MP, Mecucci C, Reisner Y, Martelli MF. 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
12. Huang XJ, Chen YH, Xu LP, Zhang YC, Liu DH, Guo NL, Lu DP. Combined transplantation of G-CSF primed allogeneic bone marrow cells and peripheral blood stem cells in treatment of severe aplastic anemia. Chin Med J (Engl) 2004; 117(4): 604–607
13. Huang XJ, Liu DH, Liu KY, Xu LP, Chen H, Han W, Chen YH, Wang JZ, Gao ZY, Zhang YC, Jiang Q, Shi HX, Lu DP. 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
14. 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
15. Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M, Gooley TA, Piantadosi S, Kaup M, Ambinder RF, Huff CA, Matsui W, Bolaños-Meade J, Borrello I, Powell JD, Harrington E, Warnock S, Flowers M, Brodsky RA, Sandmaier BM, Storb RF, Jones RJ, Fuchs EJ. 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
16. Jun HX, Jun CY, Yu ZX. *In vivo* induction of T-cell hyporesponsiveness and alteration of immunological cells of bone marrow grafts using granulocyte colony-stimulating factor. Haematologica 2004; 89(12): 1517–1524
17. Jun HX, Jun CY, Yu ZX. A direct comparison of immunological characteristics of granulocyte colony-stimulating factor (G-CSF)-primed bone marrow grafts and G-CSF-mobilized peripheral blood grafts. Haematologica 2005; 90(5): 715–716
18. Chang YJ, Huang XJ. Haploidentical SCT: the mechanisms underlying the crossing of HLA barriers. Bone Marrow Transplant 2014; 49(7): 873–879
19. Hu Y, He GL, Zhao XY, Zhao XS, Wang Y, Xu LP, Zhang XH, Yu XZ, Liu KY, Chang YJ, Huang XJ. Regulatory B cells promote graft-versus-host disease prevention and maintain graft-versus-leukemia activity following allogeneic bone marrow transplantation. OncoImmunology 2017; 6(3): e1284721
20. Zhao XS, Wang XH, Zhao XY, Chang YJ, Xu LP, Zhang XH, Huang XJ. Non-traditional $CD4^+CD25^-CD69^+$ regulatory T cells are correlated to leukemia relapse after allogeneic hematopoietic stem cell transplantation. J Transl Med 2014; 12(1): 187
21. Lu SY, Huang XJ, Liu KY, Liu DH, Xu LP. High frequency of $CD4^+CD25^-CD69^+$ T cells is correlated with a low risk of acute graft-versus-host disease in allotransplants. Clin Transplant 2012; 26(2): E158–E167
22. Lu SY, Liu KY, Liu DH, Xu LP, Huang XJ. High frequencies of $CD62L^+$ naive regulatory T cells in allografts are associated with a low risk of acute graft-versus-host disease following unmanipulated allogeneic haematopoietic stem cell transplantation. Clin Exp Immunol 2011; 165(2): 264–277
23. Lv M, Zhao XS, Hu Y, Chang YJ, Zhao XY, Kong Y, Zhang XH, Xu LP, Liu KY, Huang XJ. Monocytic and promyelocytic myeloid-derived suppressor cells may contribute to G-CSF-induced immune tolerance in haplo-identical allogeneic hematopoietic stem cell transplantation. Am J Hematol 2015; 90(1): E9–E16
24. Zhao XY, Wang YT, Mo XD, Zhao XS, Wang YZ, Chang YJ, Huang XJ. Higher frequency of regulatory T cells in granulocyte colony-stimulating factor (G-CSF)-primed bone marrow grafts compared with G-CSF-primed peripheral blood grafts. J Transl Med 2015; 13(1): 145
25. Zhao XY, Xu LL, Lu SY, Huang XJ. IL-17-producing T cells contribute to acute graft-versus-host disease in patients undergoing unmanipulated blood and marrow transplantation. Eur J Immunol 2011; 41(2): 514–526
26. Huang XJ, Han W, Xu LP, Chen YH, Liu DH, Lu J, Chen H, Zhang YC, Jiang Q, Liu KY, Lu DP. A novel approach to human leukocyte antigen-mismatched transplantation in patients with malignant hematological disease. Chin Med J (Engl) 2004; 117 (12): 1778–1785
27. Huang X, Chen Y, Han W, Chen Y, Hong H, Lu D. Human leukocyte antigen mismatched hemopietic stem cell transplants for the treatment of leukemia. J Peking Univ (Health Sci) (Beijing Da Xue Xue Bao (Yi Xue Ban)) 2003; 35(2): 115–118 (in Chinese)
28. Liu D, Huang X, Liu K, Xu L, Chen H, Han W, Chen Y, Zhang X, Jiang Q. Haploidentical hematopoietic stem cell transplantation without *in vitro* T cell depletion for treatment of hematological malignancies in children. Biol Blood Marrow Transplant 2008; 14 (4): 469–477
29. Huang XJ, Xu LP, Liu KY, Liu DH, Chen H, Han W, Chen YH, Wang JZ, Chen Y, Zhang XH, Shi HX, Lu DP. HLA-mismatched/haploidentical hematopoietic stem cell transplantation without *in vitro* T cell depletion for chronic myeloid leukemia: improved outcomes in patients in accelerated phase and blast crisis phase. Ann Med 2008; 40(6): 444–455
30. Huang XJ, Liu DH, Liu KY, Xu LP, Chen H, Han W, Chen YH, Zhang XH, Lu DP. Treatment of acute leukemia with unmanipulated HLA-mismatched/haploidentical blood and bone marrow transplantation. Biol Blood Marrow Transplant 2009; 15(2): 257–265

31. Wang Y, Liu DH, Liu KY, Xu LP, Zhang XH, Han W, Chen H, Chen YH, Wang FR, Wang JZ, Sun YQ, Huang XJ. 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
32. Chen H, Ji S, Wang H. A clinical study of haploidentical transplantation using granulocyte colony-stimulating factor stimulating donor bone marrow. Chin J Intern Med (Zhonghua Nei Ke Za Zhi) 2001; 40(11): 760–763 (in Chinese)
33. Ji SQ, Chen HR, Wang HX, Yan HM, Zhu L, Liu J, Xue M, Xun CQ. G-CSF-primed haploidentical marrow transplantation without *ex vivo* T cell depletion: an excellent alternative for high-risk leukemia. Bone Marrow Transplant 2002; 30(12): 861–866
34. Chang YJ, Wang Y, Mo XD, Zhang XH, Xu LP, Yan CH, Chen H, Chen YH, Chen Y, Han W, Wang FR, Wang JZ, Liu KY, Huang XJ. Optimal dose of rabbit thymoglobulin in conditioning regimens for unmanipulated, haploidentical, hematopoietic stem cell transplantation: long-term outcomes of a prospective randomized trial. Cancer 2017; 123(15): 2881–2892
35. Wang Y, Fu HX, Liu DH, Xu LP, Zhang XH, Chang YJ, Chen YH, Wang FR, Sun YQ, Tang FF, Liu KY, Huang XJ. Influence of two different doses of antithymocyte globulin in patients with standard-risk disease following haploidentical transplantation: a randomized trial. Bone Marrow Transplant 2014; 49(3): 426–433
36. Luo Y, Xiao H, Lai X, Shi J, Tan Y, He J, Xie W, Zheng W, Zhu Y, Ye X, Yu X, Cai Z, Lin M, Huang H. 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
37. Fu H, Xu L, Liu D, Liu K, Zhang X, Chen H, Chen Y, Han W, Wang Y, Wang J, Wang F, Huang X. Total body irradiation and cyclophosphamide plus antithymocyte globulin regimen is well tolerated and promotes stable engraftment as a preparative regimen before T cell-replete haploidentical transplantation for acute leukemia. Biol Blood Marrow Transplant 2014; 20(8): 1176–1182
38. Liu QF, Fan ZP, Zhang Y, Jiang ZJ, Wang CY, Xu D, Sun J, Xiao Y, Tan H. Sequential intensified conditioning and tapering of prophylactic immunosuppressants for graft-versus-host disease in allogeneic hematopoietic stem cell transplantation for refractory leukemia. Biol Blood Marrow Transplant 2009; 15(11): 1376–1385
39. Liu QF, Fan ZP, Wu MQ, Sun J, Wu XL, Xu D, Jiang QL, Zhang Y, Huang F, Wei YQ, Zhao J, Yu GP, Meng FY. Allo-HSCT for acute leukemia of ambiguous lineage in adults: the comparison between standard conditioning and intensified conditioning regimens. Ann Hematol 2013; 92(5): 679–687
40. Xuan L, Fan Z, Zhang Y, Zhou H, Huang F, Dai M, Nie D, Lin D, Xu N, Guo X, Jiang Q, Sun J, Xiao Y, Liu Q. Sequential intensified conditioning followed by prophylactic DLI could reduce relapse of refractory acute leukemia after allo-HSCT. Oncotarget 2016; 7 (22): 32579–32591
41. Zhang R, Shi W, Wang HF, You Y, Zhong ZD, Li WM, Zhang C, Lu X, Wang YD, Zheng P, Fang J, Hong M, Wu QL, Xia LH. Idarubicin-intensified haploidentical HSCT with GvHD prophylaxis of ATG and basiliximab provides comparable results to sibling donors in high-risk acute leukemia. Bone Marrow Transplant 2017; 52(9): 1253–1260
42. Chen Y, Wang Y, Xu LP, Liu KY, Chen H, Chen YH, Zhang XH, Wang FR, Han W, Wang JZ, Yan CH, Zhang YY, Sun YQ, Huang XJ. Haploidentical stem cell transplantation in patients aged 50 yr and older with leukemia: similar outcomes compared to younger adults. Clin Transplant 2015; 29(6): 523–530
43. Sun YQ, Xu LP, Zhang XH, Liu DH, Chen H, Wang Y, Yan CH, Wang JZ, Wang FR, Zhang YY, Liu KY, Huang XJ. A retrospective comparison of BU-fludarabine and BU-CY regimens in elderly patients or in patients with comorbidities who received unmanipulated haploidentical hematopoietic SCT. Bone Marrow Transplant 2015; 50(4): 601–603
44. Guo M, Hu KX, Yu CL, Sun QY, Qiao JH, Wang DH, Liu GX, Sun WJ, Wei L, Sun XD, Huang YJ, Qiao JX, Dong Z, Ai HS. Infusion of HLA-mismatched peripheral blood stem cells improves the outcome of chemotherapy for acute myeloid leukemia in elderly patients. Blood 2011; 117(3): 936–941
45. Zhao X, Gao F, Zhang X, Wang Y, Xu L, Liu K, Zhao X, Chang Y, Wei H, Chen H, Chen Y, Jiang Z, Huang X. Improved clinical outcomes of rhG-CSF-mobilized blood and marrow haploidentical transplantation compared to propensity score-matched rhG-CSF-primed peripheral blood stem cell haploidentical transplantation: a multicenter study. Sci China Life Sci 2016; 59(11): 1139–1148
46. Lee KH, Lee JH, Lee JH, Kim DY, Seol M, Lee YS, Kang YA, Jeon M, Hwang HJ, Jung AR, Kim SH, Yun SC, Shin HJ. Reduced-intensity conditioning therapy with busulfan, fludarabine, and antithymocyte globulin for HLA-haploidentical hematopoietic cell transplantation in acute leukemia and myelodysplastic syndrome. Blood 2011; 118(9): 2609–2617
47. Di Bartolomeo P, Santarone S, De Angelis G, Picardi A, Cudillo L, Cerretti R, Adorno G, Angelini S, Andreani M, De Felice L, Rapanotti MC, Sarmati L, Bavaro P, Papalinetti G, Di Nicola M, Papola F, Montanari M, Nagler A, Arcese W. Haploidentical, unmanipulated, G-CSF-primed bone marrow transplantation for patients with high-risk hematologic malignancies. Blood 2013; 121(5): 849–857
48. Chen J, Wang RX, Chen F, Sun AN, Qiu HY, Jin ZM, Tang XW, Han Y, Fu ZZ, He GS, Miao M, Ma X, Wu DP. Combination of a haploidentical SCT with an unrelated cord blood unit: a single-arm prospective study. Bone Marrow Transplant 2014; 49(2): 206–211
49. Gao L, Wen Q, Chen X, Liu Y, Zhang C, Gao L, Kong P, Zhang Y, Li Y, Liu J, Wang Q, Su Y, Wang C, Wang S, Zeng Y, Sun A, Du X, Zeng D, Liu H, Peng X, Zhang X. Effects of priming with recombinant human granulocyte colony-stimulating factor on conditioning regimen for high-risk acute myeloid leukemia patients undergoing human leukocyte antigen-haploidentical hematopoietic stem cell transplantation: a multicenter randomized controlled study in southwest China. Biol Blood Marrow Transplant 2014; 20(12): 1932–1939
50. Ikegame K, Yoshida T, Yoshihara S, Daimon T, Shimizu H, Maeda Y, Ueda Y, Kaida K, Ishii S, Taniguchi K, Okada M, Tamaki H, Okumura H, Kaya H, Kurokawa T, Kodera Y, Taniguchi S, Kanda Y, Ogawa H. Unmanipulated haploidentical reduced-intensity stem cell transplantation using fludarabine, busulfan, low-dose antithymocyte globulin, and steroids for patients in non-complete remission or at high risk of relapse: a prospective multicenter phase I/II study in Japan. Biol Blood Marrow Transplant 2015; 21(8):

1495–1505

51. Yahng SA, Kim JH, Jeon YW, Yoon JH, Shin SH, Lee SE, Cho BS, Eom KS, Kim YJ, Lee S, Min CK, Cho SG, Kim DW, Lee JW, Min WS, Park CW, Kim HJ. A well-tolerated regimen of 800 cGy TBI-fludarabine-busulfan-ATG for reliable engraftment after unmanipulated haploidentical peripheral blood stem cell transplantation in adult patients with acute myeloid leukemia. Biol Blood Marrow Transplant 2015; 21(1): 119–129
52. Peccatori J, Forcina A, Clerici D, Crocchiolo R, Vago L, Stanghellini MT, Noviello M, Messina C, Crotta A, Assanelli A, Marktel S, Olek S, Mastaglio S, Giglio F, Crucitti L, Lorusso A, Guggiari E, Lunghi F, Carrabba M, Tassara M, Battaglia M, Ferraro A, Carbone MR, Oliveira G, Roncarolo MG, Rossini S, Bernardi M, Corti C, Marcatti M, Patriarca F, Zecca M, Locatelli F, Bordignon C, Fleischhauer K, Bondanza A, Bonini C, Ciceri F. 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
53. Huang WR, Li HH, Gao CJ, Bo J, Li F, Dou LP, Wang LL, Jing Y, Wang L, Liu DH, Yu L. Haploidentical, unmanipulated G-CSF-primed peripheral blood stem cell transplantation for high-risk hematologic malignancies: an update. Bone Marrow Transplant 2016; 51(11): 1464–1469
54. Long H, Lu ZG, Song CY, Huang YX, Xu JH, Xu JX, Deng L, Tu SF, He YZ, Lin X, Guo KY, Wu BY. Long-term outcomes of HLA-haploidentical stem cell transplantation based on an FBCA conditioning regimen compared with those of HLA-identical sibling stem cell transplantation for haematologic malignancies. Bone Marrow Transplant 2016; 51(11): 1470–1475
55. Yang T, Lin Q, Ren J, Chen P, Yuan X, Luo X, Liu T, Zheng J, Zheng Z, Zheng X, Chen X, Zhang L, Zheng H, Chen Z, Hua X, Le S, Li J, Chen Z, Hu J. A 5-day cytoreductive chemotherapy followed by haplo-identical hsct (FA5-BUCY) as a tumor-ablative regimen improved the survival of patients with advanced hematological malignancies. Oncotarget 2016; 7(48): 78773–78786
56. Marsh JC, Ball SE, Cavenagh J, Darbyshire P, Dokal I, Gordon-Smith EC, Keidan J, Laurie A, Martin A, Mercieca J, Killick SB, Stewart R, Yin JA; British Committee for Standards in Haematology. Guidelines for the diagnosis and management of aplastic anaemia. Br J Haematol 2009; 147(1): 43–70
57. Scheinberg P, Young NS. How I treat acquired aplastic anemia. Blood 2012; 120(6): 1185–1196
58. Xu LP, Liu KY, Liu DH, Han W, Chen H, Chen YH, Zhang XH, Wang Y, Wang FR, Wang JZ, Huang XJ. A novel protocol for haploidentical hematopoietic SCT without *in vitro* T-cell depletion in the treatment of severe acquired aplastic anemia. Bone Marrow Transplant 2012; 47(12): 1507–1512
59. Xu LP, Wang SQ, Wu DP, Wang JM, Gao SJ, Jiang M, Wang CB, Zhang X, Liu QF, Xia LH, Wang X, Huang XJ. Haplo-identical transplantation for acquired severe aplastic anaemia in a multicentre prospective study. Br J Haematol 2016; 175(2): 265–274
60. Guo Z, Gao HY, Zhang TY, Liu XD, Yang K, Lou JX, He XP, Zhang Y, Chen P, Chen HR. Analysis of allogeneic hematopoietic stem cell transplantation with high-dose cyclophosphamide-induced immune tolerance for severe aplastic anemia. Int J Hematol 2016; 104(6): 720–728
61. Kojima S. Aplastic Anemia Treatment Guidelines of Asia-Pacific Hematology Consortium (APHCON). 2012. http://aphcon.org/aplastic-anemia-treatment-guidelines.html
62. Killick SB, Bown N, Cavenagh J, Dokal I, Foukaneli T, Hill A, Hillmen P, Ireland R, Kulasekararaj A, Mufti G, Snowden JA, Samarasinghe S, Wood A, Marsh JC; British Society for Standards in Haematology. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol 2016; 172(2): 187–207
63. Wang M, Dong YJ, Qiu ZX, Wang MJ, Liu W, Wang LH, Li Y, Sun YH, Xu WL, Ou JP, Wang WS, Liang ZY, Wang Q, Cen XN, Ren HY. HLA Disparity is not crucial for the survival rate and severity of chronic health conditions in adult recipients following family donor hematopoietic stem cell transplantation. Int J Hematol 2015; 101(1): 75–82
64. Huo MR, Xu LP, Li D, Liu DH, Liu KY, Chen H, Han W, Chen YH, Wang Y, Wang JZ, Zhang XH, Zhao XY, Huang XJ. The effect of HLA disparity on clinical outcome after HLA-haploidentical blood and marrow transplantation. Clin Transplant 2012; 26(2): 284–291
65. Chang YJ, Zhao XY, Xu LP, Zhang XH, Wang Y, Han W, Chen H, Wang FR, Mo XD, Zhang YY, Huo MR, Zhao XS, y K, Liu KY, Huang XJ. Donor-specific anti-human leukocyte antigen antibodies were associated with primary graft failure after unmanipulated haploidentical blood and marrow transplantation: a prospective study with randomly assigned training and validation sets. J Hematol Oncol 2015; 8(1): 84
66. Wang Y, Chang YJ, Xu LP, Liu KY, Liu DH, Zhang XH, Chen H, Han W, Chen YH, Wang FR, Wang JZ, Chen Y, Yan CH, Huo MR, Li D, Huang XJ. Who is the best donor for a related HLA haplotype-mismatched transplant? Blood 2014; 124(6): 843–850
67. Zhao XY, Chang YJ, Zhao XS, Xu LP, Zhang XH, Liu KY, Li D, Huang XJ. Recipient expression of ligands for donor inhibitory KIRs enhances NK-cell function to control leukemic relapse after haploidentical transplantation. Eur J Immunol 2015; 45(8): 2396–2408
68. Wang Y, Liu QF, Xu LP, Liu KY, Zhang XH, Ma X, Fan ZP, Wu DP, Huang XJ. Haploidentical vs identical-sibling transplant for AML in remission: a multicenter, prospective study. Blood 2015; 125(25): 3956–3962
69. Wang Y, Wang HX, Lai YR, Sun ZM, Wu DP, Jiang M, Liu DH, Xu KL, Liu QF, Liu L, Wang JB, Gao F, Ou-Yang J, Gao SJ, Xu LP, Huang XJ. Haploidentical transplant for myelodysplastic syndrome: registry-based comparison with identical sibling transplant. Leukemia 2016; 30(10): 2055–2063
70. Wang Y, Liu QF, Xu LP, Liu KY, Zhang XH, Ma X, Wu MQ, Wu DP, Huang XJ. Haploidentical versus matched-sibling transplant in adults with Philadelphia-negative high-risk acute lymphoblastic leukemia: a biologically phase III randomized study. Clin Cancer Res 2016; 22(14): 3467–3476
71. Luo XH, Chang YJ, Xu LP, Liu DH, Liu KY, Huang XJ. The impact of graft composition on clinical outcomes in unmanipulated HLA-mismatched/haploidentical hematopoietic SCT. Bone Marrow Transplant 2009; 43(1): 29–36
72. Zhao XY, Chang YJ, Xu LP, Liu DH, Liu KY, Huang XJ. Association of natural killer cells in allografts with transplant outcomes in patients receiving G-CSF-mobilized PBSC grafts and

G-CSF-primed BM grafts from HLA-haploidentical donors. Bone Marrow Transplant 2009; 44(11): 721–728

73. Chang YJ, Xu LP, Wang Y, Zhang XH, Chen H, Chen YH, Wang FR, Han W, Sun YQ, Yan CH, Tang FF, Mo XD, Liu KY, Huang XJ. Controlled, randomized, open-label trial of risk-stratified corticosteroid prevention of acute graft-versus-host disease after haploidentical transplantation. J Clin Oncol 2016; 34(16): 1855–1863
74. Ning H, Yang F, Jiang M, Hu L, Feng K, Zhang J, Yu Z, Li B, Xu C, Li Y, Wang J, Hu J, Lou X, Chen H. The correlation between cotransplantation of mesenchymal stem cells and higher recurrence rate in hematologic malignancy patients: outcome of a pilot clinical study. Leukemia 2008; 22(3): 593–599
75. Gao L, Zhang Y, Hu B, Liu J, Kong P, Lou S, Su Y, Yang T, Li H, Liu Y, Zhang C, Gao L, Zhu L, Wen Q, Wang P, Chen X, Zhong J, Zhang X. Phase II multicenter, randomized, double-blind controlled study of efficacy and safety of umbilical cord-derived mesenchymal stromal cells in the prophylaxis of chronic graft-versus-host disease after HLA-haploidentical stem-cell transplantation. J Clin Oncol 2016; 34(24): 2843–2850
76. Yan CH, Xu LP, Wang FR, Chen H, Han W, Wang Y, Wang JZ, Liu KY, Huang XJ. Causes of mortality after haploidentical hematopoietic stem cell transplantation and the comparison with HLA-identical sibling hematopoietic stem cell transplantation. Bone Marrow Transplant 2016; 51(3): 391–397
77. Huang XJ, Liu DH, Liu KY, Xu LP, Chen H, Han W. Donor lymphocyte infusion for the treatment of leukemia relapse after HLA-mismatched/haploidentical T-cell-replete hematopoietic stem cell transplantation. Haematologica 2007; 92(3): 414–417
78. Huang XJ, Liu DH, Liu KY, Xu LP, Chen YH, Wang Y, Han W, Chen H. Modified donor lymphocyte infusion after HLA-mismatched/haploidentical T cell-replete hematopoietic stem cell transplantation for prophylaxis of relapse of leukemia in patients with advanced leukemia. J Clin Immunol 2008; 28(3): 276–283
79. Mo XD, Zhang XH, Xu LP, Wang Y, Yan CH, Chen H, Chen YH, Han W, Wang FR, Wang JZ, Liu KY, Huang XJ. Salvage chemotherapy followed by granulocyte colony-stimulating factor-primed donor leukocyte infusion with graft-vs.-host disease control for minimal residual disease in acute leukemia/myelodysplastic syndrome after allogeneic hematopoietic stem cell transplantation: prognostic factors and clinical outcomes. Eur J Haematol 2016; 96 (3): 297–308
80. Yan CH, Wang Y, Wang JZ, Chen YH, Chen Y, Wang FR, Sun YQ, Mo XD, Han W, Chen H, Zhang XH, Xu LP, Liu KY, Huang XJ. Minimal residual disease- and graft-vs.-host disease-guided multiple consolidation chemotherapy and donor lymphocyte infusion prevent second acute leukemia relapse after allotransplant. J Hematol Oncol 2016; 9(1): 87
81. Yan CH, Liu DH, Liu KY, Xu LP, Liu YR, Chen H, Han W, Wang Y, Qin YZ, Huang XJ. Risk stratification-directed donor lymphocyte infusion could reduce relapse of standard-risk acute leukemia patients after allogeneic hematopoietic stem cell transplantation. Blood 2012; 119(14): 3256–3262
82. Anguille S, Lion E, Willemen Y, Van Tendeloo VF, Berneman ZN, Smits EL. Interferon-α in acute myeloid leukemia: an old drug revisited. Leukemia 2011; 25(5): 739–748
83. Mo X, Zhao X, Xu L, Liu D, Zhang X, Chen H, Wang Y, Huang X. Interferon α: the salvage therapy for patients with unsatisfactory response to minimal residual disease-directed modified donor lymphocyte infusion. Chin Med J (Engl) 2014; 127(14): 2583–2587
84. Mo XD, Zhang XH, Xu LP, Wang Y, Yan CH, Chen H, Chen YH, Han W, Wang FR, Wang JZ, Liu KY, Huang XJ. Interferon-α: a potentially effective treatment for minimal residual disease in acute leukemia/myelodysplastic syndrome after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2015; 21(11): 1939–1947
85. Yan CH, Liu QF, Wu DP, Zhang X, Xu LP, Zhang XH, Wang Y, Huang H, Bai H, Huang F, Ma X, Huang XJ. Prophylactic donor lymphocyte infusion (DLI) followed by minimal residual disease and graft-versus-host disease-guided multiple DLIs could improve outcomes after allogeneic hematopoietic stem cell transplantation in patients with refractory/relapsed acute leukemia. Biol Blood Marrow Transplant 2017; 23(8): 1311–1319
86. Sun Y, Meng F, Han M, Zhang X, Yu L, Huang H, Wu D, Ren H, Wang C, Shen Z, Ji Y, Huang X. Epidemiology, management, and outcome of invasive fungal disease in patients undergoing hematopoietic stem cell transplantation in China: a multicenter prospective observational study. Biol Blood Marrow Transplant 2015; 21(6): 1117–1126
87. Jiang X, Xu L, Zhang Y, Huang F, Liu D, Sun J, Song C, Liang X, Fan Z, Zhou H, Dai M, Liu C, Jiang Q, Xu N, Xuan L, Wu M, Huang X, Liu Q. Rituximab-based treatments followed by adoptive cellular immunotherapy for biopsy-proven EBV-associated post-transplant lymphoproliferative disease in recipients of allogeneic hematopoietic stem cell transplantation. OncoImmunology 2016; 5(5): e1139274
88. Xu LP, Jin S, Wang SQ, Xia LH, Bai H, Gao SJ, Liu QF, Wang JM, Wang X, Jiang M, Zhang X, Wu DP, Huang XJ. Upfront haploidentical transplant for acquired severe aplastic anemia: registry-based comparison with matched related transplant. J Hematol Oncol 2017; 10(1): 25
89. Mo XD, Zhao XY, Liu DH, Chen YH, Xu LP, Zhang XH, Chen H, Han W, Wang Y, Wang FR, Wang JZ, Liu KY, Huang XJ. Umbilical cord blood transplantation and unmanipulated haploidentical hematopoietic SCT for pediatric hematologic malignances. Bone Marrow Transplant 2014; 49(8): 1070–1075
90. Ciurea SO, Bayraktar UD. "No donor"? Consider a haploidentical transplant. Blood Rev 2015; 29(2): 63–70
91. Rubio MT, Savani BN, Labopin M, Piemontese S, Polge E, Ciceri F, Bacigalupo A, Arcese W, Koc Y, Beelen D, Gülbas Z, Wu D, Santarone S, Tischer J, Afanasyev B, Schmid C, Giebel S, Mohty M, Nagler A. Impact of conditioning intensity in T-replete haploidentical stem cell transplantation for acute leukemia: a report from the acute leukemia working party of the EBMT. J Hematol Oncol 2016; 9(1): 25
92. Santoro N, Ruggeri A, Labopin M, Bacigalupo A, Ciceri F, Gülbaş Z, Huang H, Afanasyev B, Arcese W, Wu D, Koc Y, Tischer J, Santarone S, Giebel S, Mohty M, Nagler A. Unmanipulated haploidentical stem cell transplantation in adults with acute lymphoblastic leukemia: a study on behalf of the Acute Leukemia Working Party of the EBMT. J Hematol Oncol 2017; 10(1): 113
93. Piemontese S, Ciceri F, Labopin M, Arcese W, Kyrcz-Krzemien S, Santarone S, Huang H, Beelen D, Gorin NC, Craddock C, Gulbas Z, Bacigalupo A, Mohty M, Nagler A; Acute Leukemia Working Party of the European Society for Blood and Marrow Transplanta-

tion (EBMT). A comparison between allogeneic stem cell transplantation from unmanipulated haploidentical and unrelated donors in acute leukemia. J Hematol Oncol 2017; 10(1): 24

94. Bashey A, Zhang MJ, McCurdy SR, St Martin A, Argall T, Anasetti C, Ciurea SO, Fasan O, Gaballa S, Hamadani M, Munshi P, Al Malki MM, Nakamura R, O'Donnell PV, Perales MA, Raj K, Romee R, Rowley S, Rocha V, Salit RB, Solh M, Soiffer RJ, Fuchs EJ, Eapen M. Mobilized peripheral blood stem cells versus unstimulated bone marrow as a graft source for T-cell-replete haploidentical donor transplantation using post-transplant cyclophosphamide. J Clin Oncol 2017; 35(26): 3002–3009
95. Mancusi A, Ruggeri L, Urbani E, Pierini A, Massei MS, Carotti A, Terenzi A, Falzetti F, Tosti A, Topini F, Bozza S, Romani L, Tognellini R, Stern M, Aversa F, Martelli MF, Velardi A. Haploidentical hematopoietic transplantation from KIR ligand-mismatched donors with activating KIRs reduces nonrelapse mortality. Blood 2015; 125(20): 3173–3182
96. Handgretinger R. Haploidentical transplantation: the search for the best donor. Blood 2014; 124(6): 827–828
97. Passweg JR, Baldomero H, Bader P, Bonini C, Duarte RF, Dufour C, Gennery A, Kröger N, Kuball J, Lanza F, Montoto S, Nagler A, Snowden JA, Styczynski J, Mohty M. 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
98. Champlin R. Now everyone has a donor for HSCT. Blood 2011; 118(2): 218
99. Wang Y, Wu DP, Liu QF, Xu LP, Liu KY, Zhang XH, Xu Y, Huang F, Huang XJ. Donor and recipient age, gender and ABO incompatibility regardless of donor source: validated criteria for donor selection for haematopoietic transplants. Leukemia 2018; 32 (2): 492–498
100. Piemontese S, Ciceri F, Labopin M, Bacigalupo A, Huang H, Santarone S, Gorin NC, Koc Y, Wu D, Beelen D, Tischer J, Ehninger G, Arcese W, Nagler A, Mohty M; Acute Leukemia Working Party (ALWP) of the European Group for Blood and Marrow Transplantation (EBMT). A survey on unmanipulated haploidentical hematopoietic stem cell transplantation in adults with acute leukemia. Leukemia 2015; 29(5): 1069–1075
101. Locatelli F, Merli P, Pagliara D, Li Pira G, Falco M, Pende D, Rondelli R, Lucarelli B, Brescia LP, Masetti R, Milano GM, Bertaina V, Algeri M, Pinto RM, Strocchio L, Meazza R, Grapulin L, Handgretinger R, Moretta A, Bertaina A, Moretta L. Outcome of children with acute leukemia given HLA-haploidentical HSCT after αβ T-cell and B-cell depletion. Blood 2017; 130(5): 677–685