Review Article

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Haploidentical hematopoietic transplantation without T-cell depletion: current status and future perspectives

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Abstract: Human leukocyte antigen (HLA)-haploidentical hematopoietic stem cell transplantation (HLA-haplo HSCT) without T-cell depletion has tremendously progressed over the past 20 years and has become a feasible treatment option for leukemia patients without an HLA-identical sibling donor. Advances in conditioning regimens, graft manipulation, and pharmacological graft-versus-host disease (GVHD) prophylaxis have reduced the risk of fatal graft failure and severe GVHD, two of the most serious complications of traversing the HLA barrier. According to clinical observations, killer immunoglobulin-like receptor (KIR) mismatch and donor-specific anti-HLA (DSA) antibodies—negative status play potential roles in reducing the risk of GVHD and graft failure following HLA-haploidentical SCT. New strategies to improve transplant outcomes include donor lymphocyte, NK cell and selected T-cell subset infusion, mesenchymal stem cell (MSC) co-transplantation and interleukin-2 (IL-2) application. Future challenges remain in improving post-transplant immune reconstitution and finding the best approach to reduce the incidence and severity of GVHD while simultaneously preserving the graft-versus leukemia effect to prevent the recurrence of underlying malignancy.

Keywords: Hematopoietic stem cell transplantation; haploidentical; graft-versus-host disease (GVHD); relapse

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Human leukocyte antigen (HLA)-haploidentical hematopoietic stem cell transplantation (HLA-haplo HSCT) is an alternative transplant option for the majority of patients with hematological disease and is available without search or acquisition costs to the patient (1-7). Over the past 2 decades, many haploidentical transplantation protocols, including T cell-replete and T cell-depleted (TCD) haplotype HSCT, depending on whether the allografts have been engineered *in vitro*, have demonstrated promising clinical outcomes (8-10). Several transplant centers have reported success with the transplantation of TCD peripheral blood stem cells (PBSCs) with a low rate of graft-versus-host disease (GVHD); however, serious infections and disease relapses resulting from delayed immune reconstitution remain the 2 most frequent causes of mortality after allogeneic HSCT, particularly in patients who receive extensive TCD $CD34^+$ cell megadose allografts (5,11-14). Therefore, many centers actively pursue bone marrow transplantation without T-cell depletion using unmanipulated haploidentical transplant protocols (6-9,15-17). The approaches used include anti-thymocyte globulin (ATG) preparative regimens for partial *in vivo* T-cell depletion, granulocyte colony-stimulating factor (G-CSF)—primed grafts to polarize the T-cell response to a Th2-type pattern, and high-dose post-transplant cyclophosphamide (Cy) to preferentially deplete alloreactive T cells (17-21). In this review, we summarize advances in the development of new conditioning regimens, improvements in GVHD prophylaxis, the incidences of invasive fungal disease (IFD) and cytomegalovirus (CMV) infection after transplantation, and strategies to improve transplant outcomes. In addition, we discuss the future

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directions of unmanipulated HLA-haplo HSCT.

Conditioning regimen of unmanipulated haploidentical transplantation

Transplant procedures using a myeloablative conditioning regimen

Peking University in China investigated the combination of G-CSF-primed bone marrow and peripheral blood with intensive immunosuppression using ATG for *in vivo* T-cell depletion. Other drugs in the conditioning regimen included cytosine arabinoside (Ara-C), busulfan (Bu), Cy, and semustine, and GVHD prophylaxis included cyclosporine (CsA), mycophenolate mofetil (MMF), and short-course methotrexate (MTX) (18). In the first report, the authors compared the clinical outcomes of HLA-haploidentical transplantation with those of HLA-matched sibling transplantation without ATG administration. The cumulative incidence of grade II to IV acute GVHD (aGVHD) was 32% and 40% in matched sibling and haploidentical transplants, respectively (P=0.13). Surprisingly, treatment-related mortality (TRM) was similar (14% *vs.* 22%), as were the relapse rate and overall survival (OS) (13% *vs.* 18% and 72% *vs.* 71%, respectively). In an updated report, Huang *et al.* reported encouraging clinical outcomes in 145 Ph^+ acute lymphoblastic leukemia patients and 450 acute myeloid leukemia patients who underwent unmanipulated HLA-haplo HSCT with the following conditioning regimen: total body irradiation (TBI) + methyl-N-(2-chloroethyl)-N-cyclohexyl-N-nitrosourea (Me-CCNU) + Ara-C + Cy + ATG and Bu + Me-CCNU + Ara-C + Cy + ATG. The 3-year probability of leukemia-free survival (LFS) in AML patients was 74%, and the 5-year probability of LFS in Ph^+ ALL patients was 65.8% (15,22). The results indicate that unmanipulated HLA-haplo HSCT produces outcomes similar to those of identical sibling donor HSCT.

A multicenter randomized controlled trial in southwest China studied the outcomes of unmanipulated HLA-haplo HSCT in high-risk AML patients using a combination of G-CSF priming during the chemotherapy conditioning regimen. G-CSF at 5 mg/kg daily was administered subcutaneously on days –10 to –7 of the chemotherapy-based conditioning regimen, which comprised CCNU 200 mg/m^2 orally on day –9, high-dose Ara-C (4 g/m^2) daily on days –8 to –7, Bu 3.2 mg/kg daily on days –6 to –4, and Cy 1.8 g/m^2 daily on days –3 to –2 (23). Based on the known activities of G-CSF (24,25), the use of G-CSF-mobilized PBSCs and enhanced leukemic chemosensitization with the combination of high-dose Ara-C plus G-CSF priming in the conditioning regimen (25-28) is expected to decrease GVHD and leukemia relapse.

Transplant procedures using non-myeloablative (NMA) conditioning regimens

Although the incidences of graft failure and GVHD have been reduced through the use of myeloablative conditioning regimens, these procedures remain associated with high regimen-related toxicity and TRM, mainly due to infectious complications, thereby limiting the applicability of haploidentical transplantations to the majority of patients. Therefore, the use of NMA conditioning regimens has been tested in multiple studies, with encouraging results (29).

Most NMA conditioning regimens incorporate the highly immunosuppressive drug fludarabine (Flu) (28). Studies from Tubingen, Germany and from Duke University in the United States have combined Flu-based conditioning with *in vivo* TCD using OKT3 (30) or CAMPATH (31) to enable the engraftment of HLA-haploidentical stem cells. These regimens were associated with acceptable non-hematologic toxicities and sustained donor cell engraftment in patients up to 66 years of age. OS at 1 year after transplantation ranged from 31% to 37% (32,33), establishing the feasibility of HLA-haploidentical HSCT after NMA conditioning.

Recently, a prospective, multicenter phase I/II study of unmanipulated, reduced-intensity HLA-haplo HSCT using a low dose of ATG and steroid was conducted in 5 institutions in Japan (34). The study enrolled 34 patients with hematologic malignancies who exhibited advanced stage disease or who were at a high risk of relapse at the time of transplantation. The conditioning regimen comprised Flu, Bu, and ATG (Fresenius, 8 mg/kg), and GVHD prophylaxis comprised tacrolimus (Tac) and methylprednisolone (1 mg/kg). Thirty-three patients achieved donor-type engraftment. The cumulative incidences of grade II to IV aGVHD and extensive cGVHD were 30.7% and 20%, respectively. Fourteen patients (41.2%) exhibited relapse. The cumulative incidence of TRM at 1 year after transplantation was 26.5%. The survival rates at 1 year for patients with complete remission (CR)/chronic phase (n=8) and non-CR (n=26) statuses before transplantation were 62.5% and 42.3%, respectively. This transplantation protocol is safe and feasible if a suitable

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donor is not available in a timely manner.

GVHD prevention of unmanipulated haploidentical transplantation

G-CSF-primed bone marrow (G-BM) and peripheral blood stem cells (G-PB)

G-CSF can induce T-cell hyporesponsiveness and a skewing toward a Th2 phenotype through an increase in plasmacytoid dendritic cells and a decrease in CD28-CD80/86 signaling (35-38). Based on these findings, the Chinese researchers Huang *et al.* developed a HLA-haplo HSCT protocol using myeloablative conditioning, intensified immunologic suppression with ATG, and a donor graft comprising G-CSF-primed bone marrow and PBSCs (17,18,23,35,38-40). Their most recent update included 450 acute leukemia patients (15), 231 (51.3%) of whom were assigned to undergo unmanipulated HLA-haplo HSCT. In this group, donors were treated with G-CSF 5 mg/kg/day subcutaneously; BM cells were harvested on the fourth day of G-CSF, and PBSCs were collected on the fifth day. GVHD prophylaxis included CsA, MMF, ATG and methotrexate. The cumulative incidence of grades II to IV and III to IV aGVHD were 36% and 10%, respectively. The cumulative incidence of cGVHD was 42% at 1 year, and the 3-year disease-free survival (DFS) and OS rates were 74% and 79%, respectively (15).

Short-term Tac

The calcineurin inhibitor Tac possesses a 100-fold higher *in vitro* inhibitory activity against T cells compared with CsA and has been used for GVHD prophylaxis both alone and in combination with other immunosuppressive agents in patients undergoing HLA-matched HSCT (41,42). A low dose of Tac has been shown to induce functional regulatory T cells (Tregs) (43). Both Tac and MMF dampen Th1-related gene transcription and preserve Treg/Th2 phenotypes (44). Our previous retrospective single-arm studies demonstrated the feasibility of the decreasing stepwise addition of Tac in GVHD prophylaxis in patients undergoing HSCT with HLA-haplo donors. However, the long-term use of Tac led to an increased incidence of infection, especially CMV infection (45). Based on our previous study, we tested a short-term Tac protocol combined with MTX and MMF compared with a classical CsA + MTX + MMF for GVHD prophylaxis in patients undergoing HSCT from HLA-haplo donors. The 100-day cumulative incidences of grade III to IV aGVHD in patients receiving the short-term Tac regimen *vs.* the CsA regimen were 29.1% *vs.* 50.0% (P=0.005) and 3.6% *vs.* 13.5% (P=0.027), respectively. No significant differences were found between the two groups in the incidences of cGVHD, relapse, and CMV infection or in DFS and OS. Lymphocyte subset analysis revealed that the number of T cells decreased to a lesser extent in the short-term Tac regimen within 3 months of transplantation (unpublished data). Thus, the short-term addition of Tac for GVHD prophylaxis in patients undergoing HLA-haplo HSCT is associated with a low incidence and decreased severity of aGVHD and does not increase the incidences of relapse and CMV infection.

Post-transplantation cyclophosphamide (PT/Cy)

PT/Cy is an attractive approach for crossing the HLA barrier in allo-HSCT because the treatment is cheap and strikingly effective and requires no special expertise beyond intravenous (IV) chemotherapy administration. A number of mechanisms likely contribute to the establishment of bi-directional tolerance by PT/Cy, and these multistep process likely proceeds through several distinct and sequential phases. The first step includes the selective killing of proliferating alloantigen-stimulated T cells. Several lines of evidence support the differential sensitivity of naive T cells versus effector (Teff)/memory T cells to Cy-mediated killing. The relative resistance of donor Teff/memory T cells to PT/Cy, as demonstrated in mice, may contribute to the overall long-term reconstitution of peripheral T-cell pools and immune competence (46). These processes are important, given the slow recovery of thymic and T-cell functions after transplantation. The second step in the process of PT/Cy-induced tolerance includes the central deletion of donor HSC-derived anti-host T cells in the thymus. This mechanism, which is advantageous because it cannot be broken with TLR ligation and/or infections, is essential for maintaining lifelong tolerance after allografting. The existence of intrathymic clonal deletion after PT/Cy was also confirmed using superantigen-disparate murine allo-combinations, which is a well-studied system used to explain self-tolerance (46). In the final key step of PT/Cy tolerance, a late breakdown of clonal deletion and an emergence of regulatory or suppressive T cells occur (20). The notion that $CD4^+$ Tregs may also contribute to Cy-induced tolerance is consistent with recent observations that

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Foxp3$^+$Tregs are critical for tolerance induction in MHC-matched and MHC-mismatched models using anti-T-cell abs and co-stimulatory blockade (47).

Based on promising preclinical results, clinical trials of HLA-haplo HSCT using PT/Cy have been performed at many transplant centers. Luznik *et al.* (48) administered 100 mg/kg PT/Cy over days +3 and +4 after a reduced-intensity conditioning (RIC) regimen. The cumulative incidences of grades II–IV and grades III–IV aGVHD by day 200 were 34% and 6%, respectively, and the cumulative incidence of extensive cGVHD was 5%. Actuarial OS and event-free survival (EFS) at 2 years after transplantation were 36% and 26%, respectively. PT/Cy as GVHD prophylaxis was initially developed for haploidentical BMT after RIC, but several recent small studies have extended the approach to myeloablative conditioning and to the use of PBSCs as the graft source. Recently, Bacigalupo *et al.* (49) reported 148 patients with hematologic malignancies who received an unmanipulated HLA-haplo HSCT followed by PT/Cy. All patients underwent myeloablative conditioning comprising thiotepa + Bu + Flu or TBI + Flu. GVHD prophylaxis comprised PT/Cy on days +3 and +5, CsA (from day 0), and MMF (from day +1). The cumulative incidences of grades II-IV and III-IV aGVHD were 24% and 10%, respectively, and the incidence of moderate to severe cGVHD was 12%. The actuarial 22 months OS was 77% for CR1 patients, 49% for CR2 patients and 38% for patients grafted in relapse (P<0.001). The study suggests that a myeloablative conditioning regimen followed by unmanipulated HLA-haplo HSCT with PT/Cy results in a low risk of acute and chronic GVHD and in encouraging TRM and overall survival rates.

IFD and CMV infection after transplantation

IFD incidence after transplantation

Due to the poor post-transplant immune reconstitution for HLA-haplo HSCT with ex vivo TCD, IFD is an important cause of morbidity and infection-related mortality (50). According to a study of 205 patients from Perugia (51), the risk of invasive aspergillosis (IA) after haploidentical transplantation with TCD was 2.7-fold higher than that after HLA-matched transplantation. Unmanipulated HLA-haplo HSCT included ATG preparative regimens for partial *in vivo* T-cell depletion, G-CSF-primed grafts to polarize the T-cell response to a Th2-type pattern, post-transplantation rapamycin to favor regulatory T-cell population development, or high-dose post-transplant Cy to preferentially deplete allo-reactive T cells (15,18,22,45,48,49). Huang *et al.* (52) reported a head-to-head comparative study performed at a single center to assess whether the above-described strategies helped to reduce the IDF incidence. Of the 1,042 consecutive patients enrolled, 390 received the HLA-matched HSCT, and 652 received unmanipulated HLA-haplo HSCT. IFD was evaluated according to the revised EORTC/MSG criteria, and only proven and probable cases were included. A total of 61 (5.8%) patients had IFD, including 15 proven cases and 46 probable cases. The IFD incidence after unmanipulated HLA-haplo HSCT was significantly higher than that after HLA-matched transplantation (7.1% *vs.* 3.3%, respectively; P=0.007). IFD occurred later in patients receiving HLA-matched transplantation compared with patients receiving unmanipulated HLA-haplo HSCT (141.5 *vs.* 23 days, respectively; P=0.04). In multivariate analysis, aGVHD grades III to IV, extensive cGVHD and haploidentical transplantation were identified as significant risk factors associated with IFD. The prognosis of IFD was not associated with the type of transplantation. These results demonstrate that more active IFD prophylactic strategies should be adopted in the setting of unmanipulated HLA-haplo HSCT.

CMV infection after transplantation

CMV infection after HLA-haplo HSCT continues to adversely affect transplant outcomes (53-55) despite the use of prophylactic or preemptive treatment (56). Peking University researchers developed the GIAC protocol for HLA-haplo HSCT and observed that patients undergoing HLA-haplo HSCT had a higher 100-day cumulative CMV antigenemia incidence compared with a matched group (65% versus 39%), whereas the CMV-associated interstitial pneumonia incidence was the same in both groups (17% in both) (18). In Japan, Kurokawa *et al.* (57) conducted HLA-haplo HSCT on 66 adults with hematologic malignancies using RIC without TCD. CMV antigenemia occurred in 45 of 57 evaluable patients at a median of 19 days after transplantation. CMV-related diseases were diagnosed in 3 patients, and one patient died of CMV colitis.

Immune reconstitution of the immune subsets likely has the greatest impact on clinical outcomes after HLA-haplo HSCT. In healthy CMV-seropositive individuals, high frequencies of CMV-specific CD4$^+$ and CD8$^+$ T cells that mediate the control of viral reactivation can be detected (58).

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Both the quantity and quality of CMV-specific T cell recovery are essential for the immune control of CMV infection following HSCT. A strategy of deferred antiviral therapy based on the presence of a detectable functional CMV-specific T cell response at the time of CMV DNAemia documentation was clinically applied, allowing for the sparing of antiviral treatment in transplant patients (59). The process of immune reconstitution is influenced by patient- and transplant-related factors, including donor and patient ages, primary disease, transplant type, conditioning regimen, stem cell source, HLA disparity, GVHD, and infection (60). A recent study indicates that the selection of a young donor, the use of stem cells derived from PBSC or G-BM/PB, the occurrence of subclinical CMV reactivation while on antiviral therapy, the avoidance of GVHD, and the use of a decreased steroid dose can improve CMV-specific immune reconstitution (61).

Strategies to improve transplant outcomes

Donor selection

Most patients have more than 1 potential haploidentical donor, and various factors have been implicated in selecting the most suitable donor for HLA-haplo HSCT. Among these factors, killer immunoglobulin-like receptor (KIR) mismatch and donor-specific anti-HLA (DSA) antibodies are the main factors to be considered.

KIR mismatch between recipients and donors has been associated with improved outcomes after HLA-haplo HSCT in several studies (62,63). Ruggeri *et al.* (62) reported improved graft rejection, GVHD, and disease relapse rates among AML patients who received stem cells from donors with KIR mismatches in the GVH direction compared with those who did not. More recently, Symons *et al.* (63) reported similar results in a cohort of 86 patients with various hematologic malignancies who underwent unmanipulated HLA-haplo HSCT with non-myeloablative conditioning and PT/Cy with improved NRM, OS, and EFS among those transplanted with KIR-mismatch donors compared with those without KIR-mismatch donors (63). Although NK cell alloreactivity likely plays a role in the success of HLA-haplo HSCT, further studies are required to better define the role of KIR mismatch in donor selection and to exploit NK alloreactivity to improve post-transplantation outcomes.

The presence of DSA by the cross-matching technique is considered an absolute contraindication to the use of that donor due to the indicated increased risk of graft failure (64). Three assays are available for measuring the presence of antibodies against donor HLA molecules: (I) lymphocytotoxic cross-matching; (II) flow cytometric cross-matching; and (III) a solid-phase immunoassay (SPI) using fluorochrome-conjugated beads coated with single HLA molecules. The SPI is the most sensitive test for DSA (65). Recently, Ciurea *et al.* (66) analyzed 122 haploidentical transplant recipients prospectively tested for DSA. Retrospective analysis to detect C1q binding DSA (C1q + DSA) was performed on 22 allo-sensitized recipients. The presence of C1q+DSA was labeled as C1q positive, and the absence of C1q + DSA was labeled as C1q negative. Of the 122 patients, 22 (18%) had DSA, 19 of whom were women (86%). Seven patients with DSA (32%) rejected the graft. The median DSA level at the time of transplant for patients who failed to engraft was 10,055 mean fluorescence intensity (MFI) *vs.* 2,065 MFI for those who engrafted (P=0.007). According to this study, patients with high DSA levels (>5,000 MFI) appear to be at a much higher risk of primary graft failure. The presence of C1q + DSA should be assessed in allo-sensitized patients before HSCT, as reducing C1q + DSA levels might prevent engraftment failure in HSCT.

Donor lymphocyte infusion (DLI)

A few studies have investigated DLI after HLA-haplo HSCT. Lewalle *et al.* (67) proposed that 10^5 cells/kg should be the starting dose for DLI in patients undergoing HLA-haplo HSCT. In a study conducted in Israel, 28 patients received prophylactic (n=6) or therapeutic DLI (n=22) in doses ranging from 1×10^2 to 1.5×10^9 T cells/kg (68). A clinical response to therapeutic DLI was observed in 6 of 22 (27.3%) patients; a greater tumor burden was correlated with a lower response. Huang *et al.* (69) administered G-CSF-primed DLI to prevent disease recurrence. The authors analyzed the data of 88 patients with advanced-stage acute leukemia after unmanipulated HLA-haplo HSCT whose treatment did (n=61) or did not (n=27) include G-CSF-primed DLI. The 2-year cumulative incidences of relapse in patients receiving prophylactic DLI *vs.* those not receiving prophylactic DLI was 36% and 55% (P=0.017), respectively. Estimated OS and EFS at 3 years for patients receiving or not receiving prophylactic DLI were 31% *vs.* 11% and 22% *vs.* 11%, respectively (P=0.001 and 0.003). According to multivariate analysis, the use of prophylactic DLI after transplantation was an

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independent prognostic factor for relapse. Subsequently, the authors retrospectively compared the anti-leukemic effects of chemotherapy alone and chemotherapy followed by modified DLI in patients with relapsed acute leukemia after unmanipulated HLA-haplo HSCT. In patients receiving chemotherapy followed by modified DLI, the complete remission rate was significantly higher (64.0% *vs.* 12.5%, P=0.000), the incidence of relapse was significantly lower (50.0% *vs.* 100.0%, P=0.000), and DFS was significantly improved (36.0% *vs.* 0.0%, P=0.000) compared with patients receiving chemotherapy alone (70). Zhou *et al.* (71) reported the long-term follow-up of 10 HLA-haplo HSCT patients infused with inducible human caspase 9-modified T (iC9-T) cells *in vivo* . These patients displayed immediate and sustained protection from major pathogens, including CMV, adenovirus, BK virus, and Epstein-Barr virus in the absence of acute or chronic GVHD, supporting the beneficial effects of this approach to immune reconstitution after haplo-HSCT.

Donor NK cell infusion

NK cell allo-reactivity may be exploited to improve the efficacy and safety of HLA-haplo HSCT. NK cells are thought to recognize their targets through both inhibitory and activating receptors. At Duke University Medical Center, 14 matched and 16 mismatched transplanted patients received a total of 51 NK cell-enriched DLIs. Long-term responders with multiple NK cell-enriched infusions and improved T cell phenotypic recovery exhibited improved durations of response and OS (72). Based on this exciting result, several studies evaluated the feasibility of NK cell infusions after HLA-haplo HSCT to utilize innate immunity against different tumors. Recently, the success of clinical-grade NK cell purification demonstrated that NK cell infusion is a promising method for prophylaxis and/or therapy for relapse after HLA-haplo HSCT (73). Yoon *et al.* (74) reported a series of 14 patients with acute leukemia or myelodysplastic syndromes who were infused with donor NK cells derived from $CD34^+$ hematopoietic cells 6 to 7 weeks after TCR HLA-haplo HSCT. No acute side effects occurred, and 4 patients developed cGVHD. Four patients were alive and disease-free 18 to 21 months post-transplantation. Two patients with active leukemia who received an NK cell infusion did not respond. Recently, Choi *et al.* (75) reported a series of 41 patients with hematologic malignancies who underwent HLA-haplo HSCT after reduced-intensity conditioning. The NK cells were infused into patients twice at 2 and 3 weeks after HSCT at an escalating dose from 2 to 10×10^7 cells/kg of body weight or available cells. At all dose levels, no acute toxicity was observed after NK cell infusion. No significant differences were found in the cumulative incidences of major HSCT outcomes, including engraftment, grade II to IV aGVHD, moderate to severe cGVHD, and TRM, in patients who received HLA-haplo HSCT and subsequent donor NK cell infusion compared to 31 historical patients who underwent HLA-haplo HSCT after the same conditioning regimen but without high-dose NK cell infusion. However, a significant reduction was observed in leukemia progression (46% to 74%), and post-transplantation NK cell infusion was identified as an independent predictor of decreased leukemia progression (hazard ratio, 0.527). Prospective studies are required to explore the use of NK cells post-HLA-haplo HSCT.

Selected T-cell subset infusions

As an alternative approach to unmodified donor T cell infusions, several groups have tested the feasibility of donor T-cell infusions that were depleted of allo-reactive T cells (76-79) or that were introduced with a herpes simplex thymidine kinase suicide gene, allowing the allo-reactive T cells to be killed in the case of severe GVHD (80). In the haploidentical setting, Amrolia *et al.* (81) used an anti-CD25 immunotoxin to deplete allo-reactive lymphocytes and infused allo-depleted donor T cells after ex vivo TCD haploidentical transplantation. Viral-specific responses were observed in 4 of 6 evaluable patients receiving higher doses of T cells with a low incidence of severe GVHD. Interestingly, loss of the HLA haplotype that differed from the donor's haplotype in leukemic cells was recently reported in patients who relapsed after haploidentical transplantation and donor T cells infusion, indicating that escape from donor alloreactive T-cell killing represents one mechanism underlying leukemia relapse (82). Therefore, the status of mismatched HLA on relapsed leukemic cells may require examination before the utility of additional donor T-cell infusions is explored. In a study from Perugia (83), 28 patients with high-risk hematologic malignancies received myeloablative conditioning followed by 2×10^6/kg freshly isolated donor Tregs. Four days later, patients received 1×10^6 conventional T lymphocytes (Tcons) and 10×10^6 highly purified $CD34^+$ cells from full haplotype donors. Although no post-transplantation immunosuppression was administered, the incidences of

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aGVHD and cGVHD were extremely low. Interestingly, the pattern of post-transplantation immune reconstitution markedly differed from that of standard TCD HLA-haplo HSCT, with the rapid recovery of T-cell subpopulations, the development of a wide T-cell repertoire, and high frequencies of antigen-specific $CD4^+$ and $CD8^+$ lymphocytes. Significantly fewer CMV reactivation episodes and no CMV disease-related deaths occurred. Their innovative method of infusing regulatory T cells enabled the administration of larger amounts of mature T cells, which may lead to earlier immune reconstitution and improved outcomes.

Application of mesenchymal stem cells (MSCs)

Numerous studies have demonstrated that MSCs exhibit profound immune-modulatory functions both *in vitro* and *in vivo* (84). MSCs modulate the proliferation, activation, and maturation of T and B lymphocytes *in vitro* in a dose-dependent and time-limited manner (85,86). In adult patients undergoing transplantation from an HLA-identical sibling, MSC infusion is safe and possibly accelerates hematopoietic recovery and reduces the incidences of both acute and chronic GVHD. Lazarus *et al.* (87) previously demonstrated that the co-transplantation of MSCs with HSC is feasible and appears to be safe, without immediate or late MSC-associated transfusion toxicities. The sustained donor engraftment observed in patients treated with MSCs compared favorably to the risk of rejection observed in HLA-haplo HSCT recipients. Ball *et al.* (88) co-transplanted donor-derived MSCs in 14 children undergoing TCD haploidentical transplantation. None of the patients who received MSCs experienced either an adverse reaction or a graft failure. Additionally, Zhou *et al.* (89) and Weng *et al.* (90) also suggested that the transfusion of *in vitro*-expanded MSCs is a safe and effective salvage therapy for patients with steroid-resistant cGVHD. Our groups evaluated the safety and cGVHD prophylaxis efficacy of discontinuous MSC infusion in patients following unmanipulated HLA-haplo HSCT. We found decreased 2-year cumulative incidences of both cGVHD and severe lung cGVHD. After MSC transfusion, the number of NK cells decreased, but the number of memory B lymphocytes and the ratio of Th1:Th2 increased (unpublished data).

Application of interleukin-2 (IL-2)

IL-2, a pleiotropic cytokine, plays a central role in immune responses. The administration of IL-2 early after HSCT during minimal residual disease might reduce the relapse rate and increase the immunocompetence of these patients (91). This effect could be due to a lymphoid orientation of primitive $CD34^+CD105^+$ cells expressing high-affinity IL-2 receptors. Thus exogenous IL-2 might lead to an enhancement of the graft-versus leukemia (GVL) effect (92). Liu *et al.* (93) studied 19 patients with acute lymphoblastic malignancy, including 6 patients receiving allografts from haploidentical donors, who underwent IL-2 treatment for a high probability of disease recurrence after allo-HSCT. After a median follow-up of 6 months (range, 3-19 months), 14 of 15 evaluable patients in the cohort were disease free (93.33%), whereas one patient in the 'high-risk' pre-transplantation category relapsed. The toxicities from IL-2 mainly included fever, pain, redness and swelling at the injection site. The authors concluded that the subcutaneous administration of low-dose IL-2 for 100 days or more could represent a safe and effective strategy for preventing relapse in acute lymphoblastic malignancy patients with a high risk of recurrence after unmanipulated allo-HSCT.

Future directions

Over the past several years, unmanipulated HLA-haplo HSCT has been adopted by increasing numbers of transplant centers worldwide (9,15,23,33,94-96). Unmanipulated HLA-haplo HSCT provides an opportunity for patients to benefit from HSCT when an HLA-matched donor is not available. The final goal of HLA-haplo HSCT is to successfully overcome the HLA barrier and capture an optimal GVL effect with moderate GVHD. Several novel approaches exist that may be promising in the future: (I) selective but effective allo-depletion, which facilitates successful donor engraftment and improved post-transplant immune reconstitution while reducing the incidence of GVHD; (II) improved DLI to achieve a GVL effect without or with limited GVHD; (III) adoptive cellular immunotherapy with cells such as Tregs, NK/Tregs, MSCs and donor-derived NK cells as well as third-party cell infusion; and (IV) pathogen- or leukemia-specific donor-derived T cell infusion, which could represent an additional approach for preventing opportunistic infection and reducing the leukemia relapse rate after HLA-haplo HSCT.

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Footnote

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References

1. Bashey A, Zhang X, Sizemore CA, et al. T-cellreplete 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;31:1310-6.
2. Chang YJ, Huang XJ. Haploidentical bone marrow transplantation without T-cell depletion. Semin Oncol 2012;39:653-63.
3. Di Bartolomeo P, Santarone S, De Angelis G, et al. Haploidentical, unmanipulated, G-CSF-primed bone marrow transplantation for patients with high-risk hematologic malignancies. Blood 2013;121:849-57.
4. Lv M, Huang XJ. Allogeneic hematopoietic stem cell transplantation in China: where we are and where to go. J Hematol Oncol 2012;5:10.
5. Reisner Y, Hagin D, Martelli MF. Haploidentical hematopoietic transplantation: current status and future perspectives. Blood 2011;118:6006-17.
6. Huang XJ, Zhu HH, Chang YJ, et al. The superiority of haploidentical related stem cell transplantation over chemotherapy alone as postremission treatment for patients with intermediate- or high-risk acute myeloid leukemia in first complete remission. Blood 2012;119:5584-90.
7. Zhao Y, Huang H, Wei G. Novel agents and biomarkers for acute lymphoid leukemia. J Hematol Oncol 2013;6:40.
8. 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;38:291-7.
9. 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;43:98-104.
10. Aversa F. Setting the standard in T-cell-depleted haploidentical transplantation and beyond. Best Pract Res Clin Haematol 2011; 24: 325-9.
11. 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;84:3948-55.
12. Mulanovich VE, Jiang Y, de Lima M, et al. Infectious complications in cord blood and T-cell depleted haploidentical stem cell transplantation. Am J Blood Res 2011;1:98-105.
13. Kang Y, Chao NJ, Aversa F. Unmanipulated or CD34 selected haplotype mismatched transplants. Curr Opin Hematol 2008;15: 561-7.
14. Aversa F, Terenzi A, Tabilio A, et al. Full haplotypemismatched hematopoietic stem-cell transplantation: a phase II study in patients with acute leukemia at high risk of relapse. J Clin Oncol 2005;23:3447-54.
15. Wang Y, Liu QF, Xu LP, et al. Haploidentical vs identical-sibling transplant for AML in remission: a multicenter, prospective study. Blood 2015;125:3956-62.
16. Schuster FR, Meisel R, Führer M, et al. Anti-leukaemic activity of a novel haploidentical-transplantation approach employing unmanipulated bone marrow followed by CD6-depleted peripheral blood stem cells in children with refractory/relapsed acute leukaemia. Br J Haematol 2013;162:802-7.
17. Chen XH, Zhang C, Zhang X, et al. Role of antithymocyte globulin and granulocyte-colony stimulating factor-mobilized bone marrow in allogeneic transplantation for patients with hematologic malignancies. Biol Blood Marrow Transplant 2009;15:266-73.
18. 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 outcome with HLA identical sibling transplantation. Blood 2006;107:3065-73.
19. Lu RN, Miao KR, Zhang R, et al. Haploidentical hematopoietic stem cell transplantation following myeloablative conditioning regimens in hematologic diseases with G-CSF-mobilized peripheral blood stem cells grafts without T cell depletion: a single center report of 38 cases. Med Oncol 2014;31:81.
20. Luznik L, O'Donnell PV, Fuchs EJ. Post-transplantation cyclophosphamide for tolerance induction in HLA-

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haploidentical bone marrow transplantation. Semin Oncol 2012;39:683-93.
21. Bashey A, Solomon SR. T-cell replete haploidentical donor transplantation using post-transplant CY: an emerging standard-of-care option for patients who lack an HLA-identical sibling donor. Bone Marrow Transplant 2014;49:999-1008.
22. Chen H, Liu KY, Xu LP, et al. Haploidentical Hematopoietic Stem Cell Transplantation without In Vitro T Cell Depletion for the Treatment of Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Biol Blood Marrow Transplant 2015;21:1110-6.
23. Gao L, Wen Q, Chen X, et al. 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;20:1932-9.
24. Bendall LJ, Bradstock KF. G-CSF: From granulopoietic stimulant to bone marrow stem cell mobilizing agent. Cytokine Growth Factor Rev 2014;25:355-67.
25. Schuettpelz LG, Borgerding JN, Christopher MJ, et al. G-CSF regulates hematopoietic stem cell activity, in part, through activation of Toll-like receptor signaling. Leukemia 2014;28:1851-60.
26. Löwenberg B, van Putten W, Theobald M, et al. Effect of priming with granulocyte colony-stimulating factor on the outcome of chemotherapy for acute myeloid leukemia. N Engl J Med 2003;349:743-52.
27. Pabst T, Vellenga E, van Putten W, et al. Favorable effect of priming with granulocyte colony-stimulating factor in remission induction of acute myeloid leukemia restricted to dose escalation of cytarabine. Blood 2012;119:5367-73.
28. Zhang X, Li Y, Zhang Y, et al. Etoposide in combination with low-dose CAG (cytarabine, aclarubicin, G-CSF) for the treatment of relapsed or refractory acute myeloid leukemia: A multicenter, randomized control trial in southwest China. Leuk Res 2013;37:657-64.
29. Kanda J, Chao NJ, Rizzieri DA. Haploidentical Transplantation for Leukemia. Curr Oncol Rep 2010;12:292-301.
30. Bethge WA, Faul C, User M, et al. Haploidentical allogeneic hematopoietic cell transplantation in adults using CD3/CD19 depletion and reduced intensity conditioning: An update. Blood Cells Mol Dis 2008;40:13-9.
31. Liu H, Zhai X, Song Z, et al. Busulfan plus fludarabine as a myeloablative conditioning regimen compared with busulfan plus cyclophosphamide for acute myeloid leukemia in first complete remission undergoing allogeneic hematopoietic stem cell transplantation: a prospective and multicenter study. J Hematol Oncol 2013;6:15.
32. Rizzieri DA, Koh LP, Long GD, et al. Partially matched, nonmyeloablative allogeneic transplantation: clinical outcomes and immune reconstitution. J Clin Oncol 2007;25:690-7.
33. Federmann B, Bornhauser M, Beelen DW, et al. Haploidentical allogeneic hematopoietic cell transplantation in adults using CD3/CD19 depletion and reduced intensity conditioning: a phase II study. Haematologica 2012;97:1523-31.
34. Ikegame K, Yoshida T, Yoshihara S, et al. 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;21:1495-505.
35. Jun HX, Jun CY, Yu ZX. In vivo induction of T-cell hyporesponsiveness and alteration of immunological cells of bone marrow grafts using granulocyte colonystimulating factor. Haematologica 2004;89:1517-24.
36. Shier LR, Schultz KR, Imren S, et al. Differential effects of granulocyte colony-stimulating factor on marrow- and bloodderived hematopoietic and immune cell populations in healthy human donors. Biol Blood Marrow Transplant 2004;10:624-34.
37. Franzke A, Piao W, Lauber J, et al. G-CSF as immune regulator in T cells expressing the G-CSF receptor: implications for transplantation and autoimmune diseases. Blood 2003;102:734-9.
38. Arpinati M, Green CL, Heimfeld S, et al. Granulocyte-colony stimulating factor mobilizes T helper 2-inducing dendritic cells. Blood 2000;95:2484-90.
39. Lai YR, Chen YH, Hu DM, et al. Multicenter phase II study of a combination of cyclosporine, methotrexate and mycophenolate mofetil for GVHD prophylaxis: results of the Chinese Bone Marrow Transplant Cooperative Group (CBMTCG). J Hematol Oncol 2014;7:59.
40. Xiao-Jun H, Lan-Ping X, Kai-Yan L, et al. Partially matched related donor transplantation can achieve outcomes comparable with unrelated donor transplantation for patients with hematologic malignancies. Clin Cancer Res 2009;15:4777-83.
41. Jacobson P, Uberti J, Davis W, et al. Tacrolimus: a new agent for the prevention of graft-versus-host disease in

© Stem Cell Investigation. All rights reserved.

hematopoietic stem cell transplantation. Bone Marrow Transplant 1998;22:217-25.
42. Ziakas PD, Zervou FN, Zacharioudakis IM, et al. Graft-Versus-Host Disease Prophylaxis after Transplantation: A Network Meta-Analysis. PLoS One 2014;9:e114735.
43. Wang Z, Shi B, Jin H, et al. Low-dose of tacrolimus favors the induction of functional CD4(t)CD25(t)FoxP3(t) regulatory T cells in solidorgan transplantation. Int Immunopharmacol 2009;9:564-9.
44. Abadja F, Atemkeng S, Alamartine E, et al. Impact of mycophenolic acid and tacrolimus on Th17-related immune response. Transplantation 2011;92:396-403.
45. Gao L, Liu J, Zhang Y, et al. Feasibility of stepwise addition of tacrolimus as a graft-versus-host disease prophylaxis in non-T-cell-depleted haploidentical hematopoietic stem cell transplantation for patients with hematological malignancies. 2015 EBMT. Abstract 040.
46. Luznik L, Fuchs EJ. High-dose post-transplantation cyclophosphamide to promote graft-host tolerance after allogeneic hematopoietic stem cell transplantation. Immunol Res 2010;47:65-77.
47. Kendal AR, Chen Y, Regateiro FS, et al. Sustained suppression by Foxp3t regulatory T cells is vital for infectious transplantation tolerance. J Exp Med 2011;208:2043-53.
48. 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;14:641-50.
49. 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:S37-9.
50. Aversa F, Reisner Y, Martelli MF. The haploidentical option for high-risk haematological malignancies. Blood Cells Mol Dis 2008;40:8-12.
51. Cunha C, Di Ianni M, Bozza S, et al. Dectin-1 y238x polymorphism associates with susceptibility to invasive aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanisms of antifungal immunity. Blood 2010;116:5394-402.
52. Sun Y, Xu L, Liu D, et al. Incidence of invasive fungal disease after unmanipulated haploidentical stem cell transplantation was significantly higher than that after HLA-matched sibling transplantation. Clin Microbiol Infect 2013;19:1029-34.
53. Rizzieri DA, Liang PK, Long GD, et al. Partially matched, nonmyeloablative allogeneic transplantation: clinical outcomes and immune reconstitution. J Clin Oncol 2007;25:690-7.
54. George B, Pati N, Gilroy N, et al. Pre-transplant cytomegalovirus (CMV) serostatus remains the most important determinant of CMV reactivation after allogeneic hematopoietic stem cell transplantation in the era of surveillance and preemptive therapy. Transpl Infect Dis 2010;12:322-9.
55. Lin R, Liu Q. Diagnosis and treatment of viral diseases in recipients of allogeneic hematopoietic stem cell transplantation. J Hematol Oncol 2013;6:94.
56. Reusser P, Einsele H, Lee J, et al. Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. Blood 2002;99:1159-64.
57. Kurokawa T, Ishiyama K, Ozaki J, et al. Haploidentical hematopoietic stem cell transplantation to adults with hematologic malignancies: analysis of 66 cases at a single Japanese center. Int J Hematol 2010;91:661-9.
58. Kern F, Bunde T, Faulhaber N, et al. Cytomegalovirus (CMV) phosphoprotein 65 makes a large contribution to shaping the T cell repertoire in CMV-exposed individuals. J Infect Dis 2002;185:1709-16.
59. Solano C, Benet I, Remigia MJ, et al. Immunological monitoring for guidance of preemptive antiviral therapy for active cytomegalovirus infection in allogeneic stem-cell transplant recipients: a pilot experience. Transplantation 2011;92:e17-20.
60. Auletta JJ, Lazarus HM. Immune restoration following hematopoietic stem cell transplantation: an evolving target. Bone Marrow Transplant 2005;35:835-57.
61. Luo XH, Chang YJ, Huang XJ. Improving cytomegalovirus-specific T cell reconstitution after haploidentical stem cell transplantation. J Immunol Res 2014;2014:631951.
62. 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;110:433-40.
63. Symons HJ, Leffell MS, Rossiter ND, et al. Improved survival with inhibitory killer immunoglobulin receptor (KIR) gene mismatches and KIR haplotype B donors after nonmyeloablative, HLA-haploidentical bone

© Stem Cell Investigation. All rights reserved.

marrow transplantation. Biol Blood Marrow Transplant 2010;16:533-42.
64. Ciurea SO, Champlin RE. Donor Selection in T CelleReplete Haploidentical Hematopoietic Stem Cell Transplantation: Knowns, Unknowns, and Controversies. Biol Blood Marrow Transplant 2013;19:180-4.
65. Pei R, Lee JH, Shih NJ, et al. Single human leukocyte antigen flow cytometry beads for accurate identification of HLA antibody specificities. Transplantation 2003;75:43-9.
66. Ciurea SO, Thall PF, Milton DR, et al. Complement-Binding Donor-Specific Anti-HLA Antibodies and Risk of Primary Graft Failure in Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2015;21:1392-8.
67. Lewalle P, Triffet A, Delforge A, et al. et al. Donor lymphocyte infusions in adult haploidentical transplant: a dose finding study. Bone Marrow Transplant 2003;31:39-44.
68. Or R, Hadar E, Bitan M, et al. Safety and efficacy of donor lymphocyte infusions following mismatched stem cell transplantation. Biol Blood Marrow Transplant 2006;12:1295-301.
69. Wang Y, Liu DH, Xu LP, et al. Prevention of relapse using granulocyte CSF-primed PBPCs following HLA-mismatched/haploidentical, T-cell-replete hematopoietic SCT in patients with advanced-stage acute leukemia: a retrospective risk-factor analysis. Bone Marrow Transplant 2012;47:1099-104.
70. Yan CH, Wang JZ, Liu DH, et al. Chemotherapy followed by modified donor lymphocyte infusion as a treatment for relapsed acute leukemia after haploidentical hematopoietic stem cell transplantation without in vitro T-cell depletion: superior outcomes compared with chemotherapy alone and an analysis of prognostic factors. Eur J Haematol 2013;91:304-14.
71. Zhou X, Stasi AD, Tey SK, et al. Long-term outcome after haploidentical stem cell transplant and infusion of T cells expressing the inducible caspase 9 safety transgene. Blood 2014;123:3895-905.
72. Rizzieri DA, Storms R, Chen DF, et al. Natural killer cell-enriched donor lymphocyte infusions from A 3-6/6 HLA matched family member following nonmyeloablative allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2010;16:1107-14.
73. Nguyen S, Béziat V, Norol F, et al. Infusion of allogeneic natural killer cells in a patient with acute myeloid leukemia in relapse after haploidentical hematopoietic stem cell transplantation. Transfusion 2011;51:1769-78.
74. Yoon SR, Lee YS, Yang SH, et al. Generation of donor natural killer cells from CD34(+) progenitor cells and subsequent infusion after HLA-mismatched allogeneic hematopoietic cell transplantation: a feasibility study. Bone Marrow Transplant 2010;45:1038-46.
75. Choi I, Yoon SR, Park SY, et al. Donor-Derived Natural Killer Cells Infused after Human Leukocyte AntigeneHaploidentical Hematopoietic Cell Transplantation: A Dose-Escalation Study. Biol Blood Marrow Transplant 2014;20:696-704.
76. Nadal E, Fowler A, Kanfer E, et al. Adjuvant interleukin-2 therapy for patients refractory to donor lymphocyte infusions. Exp Hematol 2004;32:218-23.
77. Ge X, Brown J, Sykes M, et al. CD134- allodepletion allows selective elimination of alloreactive human T cells without loss of virusspecific and leukemia-specific effectors. Biol Blood Marrow Transplant 2008;14:518-30.
78. Bohana-Kashtan O, Morisot S, Hildreth R, et al. Selective reduction of graft-versus-host disease-mediating human T cells by ex vivo treatment with soluble Fas ligand. J Immunol 2009;183:696-705.
79. Stuehler C, Mielke S, Chatterjee M, et al. Selective depletion of alloreactive T cells by targeted therapy of heat shock protein 90: a novel strategy for control of graft-versus-host disease. Blood 2009;114:2829-36.
80. 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;10:489-500.
81. 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;108:1797-808.
82. Vago L, Perna SK, Zanussi M, et al. Loss of mismatched HLA in leukemia after stem-cell transplantation. N Engl J Med 2009;361:478-88.
83. Di Ianni M, Falzetti F, Carotti A, et al. Tregs prevent GVHD and promote immune reconstitution in HLA-haploidentical transplantation. Blood 2011;117:3921-8.
84. Ball LM, Bernardo ME, Locatelli F, et al. Potential role of mesenchymal stromal cells in pediatric hematopoietic SCT. Bone Marrow Transplant 2008;42:S60-6.
85. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 2005;105:1815-22.
86. Bartholomew A, Sturgeon C, Siatskas M, et al. Mesenchymal stem cells suppress lymphocyte proliferation

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in vitro and prolong skin graft survival in vivo. Exp Hematol 2002;30:42-8.
87. Lazarus HM, Koc ON, Devine SM, et al. Cotransplantation of HLA-Identical Sibling Culture-Expanded Mesenchymal Stem Cells and Hematopoietic Stem Cells in Hematologic Malignancy Patients. Biol Blood Marrow Transplant 2005;11:389-98.
88. Ball LM, Bernardo ME, Roelofs H, et al. Cotransplantation of ex vivo expanded mesenchymal stem cells accelerates lymphocyte recovery and may reduce the risk of graft failure in haploidentical hematopoietic stem-cell transplantation. Blood 2007;110:2764-7.
89. Zhou H, Guo M, Bian CJ, et al. Efficacy of Bone Marrow-Derived Mesenchymal Stem Cells in the Treatment of Sclerodermatous Chronic Graft-versus-Host Disease: Clinical Report. Biol Blood Marrow Transplant 2010;16:403-12.
90. Weng JY, Du X, Geng SX, et al. Mesenchymal stem cell as salvage treatment for refractory chronic GVHD. Bone Marrow Transplant 2010;45:1732-40.
91. Zhao XS, Wang XH, Zhao XY, et al. Non-traditional CD4+CD25-CD69+ regulatory T cells are correlated to leukemia relapse after allogeneic hematopoietic stem cell transplantation. J Transl Med 2014;12:187.
92. Schlegel P, Teltschik HM, Pfeiffer M, et al. Long-term IL-2 therapy after transplantation of T cell depleted stem cells from alternative donors in children. Best Pract Res Clin Haematol 2011;24:443-52.
93. Liu KY, Chen YH, Liu DH, et al. A pilot study of low-dose recombinant interleukin-2 for acute lymphoblastic malignancy after unmanipulated allogeneic blood and marrow transplantation. Bone Marrow Transplant 2008;42:535-9.
94. Huang XJ. Current status of haploidentical stem cell transplantation for leukemia. J Hematol Oncol 2008;1:27.
95. Lee KH, Lee JH, Kim DY, et al. Reduced-intensity conditioning therapy with busulfan, fludarabine, and antithymocyte globulin for HLA-haploidentical hematopoietic cell transplantation in acute leukemia and myelodysplastic syndrome. Blood 2011;118:2609-17.
96. Kasamon YL, Luznik L, Leffell MS, et al. Nonmyeloablative HLA-haploidentical bone marrow transplantation with high-dose posttransplantation cyclophosphamide: effect of HLA disparity on outcome. Biol Blood Marrow Transplant 2010;16:482-9.

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