haematologica
Journal of the Ferrata Storti Foundation

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Received: June 30, 2024.
Accepted: November 8, 2024.

Citation: Xiaodong Mo, Xuying Pei, and Xiaojun Huang. Optimization of T-cell replete haploidentical hematopoietic stem cell transplantation: the Chinese experience. Haematologica. 2024 Nov 21. doi: 10.3324/haematol.2024.286194 [Epub ahead of print]

Optimization of T-cell replete haploidentical hematopoietic stem cell transplantation: the Chinese experience

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Authors' contributions

X.-J.H. designed the review, X.-D.M. and X.-Y.P. wrote the manuscript.

Conflict of interest disclosure

The authors declare that they have no competing financial interests.

Funding

This work was supported by the National Key Research and Development Program of China (No. 2022YFC2502606), the Major Program of the National Natural Science Foundation of China (No. 82293630), the Peking University Medicine Fund for World's Leading Discipline or Discipline Cluster Development (No.71003Y3035), and the Tongzhou District Distinguished Young Scholars (No. JCQN2023009), and Plan Project of Tongzhou Municipal Science and Technology (No. KJ2024CX045), the National Natural Science Foundation of China (No. 82170208), Being Nova Program (grant number 20220484076), Beijing Natural Science Foundation (No. Z230016), Peking University People's Hospital Research and Development Funds (No. RZ2022-02).

Abstract:

Haploidentical-related donor (HID) hematopoietic stem cell transplantation (HSCT) has undergone significant advances in recent decades. Granulocyte colony-stimulating factor- and antithymocyte globulin-based protocols and post-transplantation cyclophosphamide-based regimens represent two of the current T-cell-replete protocols in HID HSCT. Recently, the optimization of several critical transplant techniques has further improved hematopoietic reconstitution, decreased the incidence of relapse and graft-versus-host disease after HID HSCT, and extended the application of HID HSCT to older patients and those with non-malignant hematologic disorders. Particularly, combining this approach with novel immunotherapy would further improve the efficacy and safety of HID HSCT. This review focuses on recent progress in the optimization of HID HSCT.

Keywords: haploidentical; antithymocyte globulin; granulocyte colony-stimulating factor; post-transplantation cyclophosphamide

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is one of the most important curative methods for hematologic malignancies.[1, 2] Human leukocyte antigen (HLA)-matched sibling donor (MSD) is the first choice for allo-HSCT; however, many patients do not have an MSD. The Peking University Institute of Hematology, using granulocyte colony-stimulating factor (G-CSF) and antithymocyte globulin (ATG), as well as the transplant group of Johns Hopkins University, using post-transplant cyclophosphamide (PTCy) to induce immune tolerance, overcame the barriers of HLA disparity, which promoted the rapid development and wide use of haploidentical-related donor (HID) HSCT. In this review, we focus on the advancements in HID HSCT optimization.

Owing to the high incidence of graft rejection and severe graft-versus-host disease (GVHD), the clinical outcomes of HID HSCT were poor before 2000. Although the protocol of T-cell depletion *in vitro* could prevent severe GVHD (Table 1), the high incidence of graft rejection and relapse significantly affected the survival of HID HSCT recipients.

Based on the immune tolerance induced by granulocyte colony-stimulating factor (G-CSF) plus ATG-based regimens, Huang et al. at Peking University established the Beijing protocol for an unmanipulated HID HSCT regimen with G-CSF-mobilized/primed grafts, which has been significantly improved after the optimization of major transplant techniques. Several multicenter prospective studies confirmed that the clinical outcomes of HID HSCT following this protocol were significantly better than those who received chemotherapies as consolidation in acute myeloid leukemia (AML)[3] or acute lymphoblastic leukemia (ALL),[4] which were similar to those who received MSD HSCT.[5-7] Currently, the Beijing protocol makes up over 90% of HID HSCT in China, and HID HSCT accounted for 63% (7977/31525) of allo-HSCT in 2019 compared to 29.6% (313/1062) in 2008 according to the report from the Chinese Blood and Marrow Transplantation Registry Group.[8, 9]

In addition, colleagues at Johns Hopkins University proposed a modality with T cell-replete and post-transplantation cyclophosphamide (PTCy)-based regimens to overcome the barrier of HLA disparity. Engraftment, GVHD, and long-term survival rates were 88–91%, 16–42%, and 40–65%,[10, 11] respectively, for HID HSCT following this protocol (Table 1). Several studies compared the efficacy and safety of HID HSCT using the Beijing and PTCy protocols, and most

clinical outcomes were comparable between the two protocols (Table 2).

To date, HID HSCT has been used worldwide, and several optimizations have further improved the efficacy and safety of this transplantation technique.

2. Optimization of hematopoietic reconstitution after HID HSCT

With the increasing use of HID HSCT, poor graft failure (PGF), defined as a hypo- or aplastic BM with 2 or 3 of the following: (1) neutrophils $\leq 0.5 \times 109/L$; (2) platelets $\leq 20 \times 109/L$; and/or (3) hemoglobin concentration ≤ 70 g/L for at least 3 consecutive days after day +28 post-HSCT or in accordance with platelets and/or red blood cell transfusion and/or G-CSF support requirement, has become one of the most important post-transplant complications. The incidence of PGF is 4–5% after HID HSCT;[12] however, it can seriously influence the quality of life and increase the risk of non-relapse mortality (NRM).

2.1 New pathogenesis-oriented approach for poor hematopoietic function after HID HSCT

The bone marrow (BM) microenvironment is critical for the regulation of hematopoietic stem cells (HSCs), and endothelial cells (ECs) play essential roles in regulating hematopoiesis.[13] Kong et al.[14] demonstrated that defective BM ECs before HSCT and impaired BM EC reconstitution at early time points after HSCT were positively correlated with oxygen species (ROS) levels, and BM EC < 0.1% before HSCT could identify high-risk patients with poor graft function after HID HSCT. In a randomized controlled trial (RCT),[15] HID HSCT recipients with a BM EC < 0.1% were randomly assigned to the N□acetyl□L□cysteine (NAC) prophylaxis group (group A) or non-prophylaxis group (group B). NAC prophylaxis improved BM ECs and $CD34^+$ cells, reduced ROS levels after HSCT, and decreased the incidence of poor graft function after HID HSCT in high-risk patients. We should emphasize that ECs dysfunction and ROS represent just one of several components contributing to the complex pathogenesis of poor graft function.

2.2 Cellular therapies for GF after HID HSCT

Secondary transplantation is the most intensive salvage cellular therapy for severe GF. Ma et al. reported a new strategy for second transplantation, including a conditioning regimen consisting of fludarabine (30 mg/m^2/day, days -6 to -2) and cyclophosphamide (1,000 mg/m^2/day, days -5 to -4), using a different HID, and using a combination of G-CSF primed BM (G-BM) and G-CSF-mobilized peripheral blood (PB) stem cells (G-PB) harvests. Compared with the historical group without the novel regimen, neutrophil engraftment (100% vs. 58.5%, P < 0.001), platelet

engraftment (75.8% vs. 32.3%, P < 0.001), and overall survival (OS) (60.0% vs. 26.4%, P = 0.011) improved in the novel regimen group.[16]

Other cellular therapies for the treatment of GF after HID HSCT have also been reported. Fei et al.[17] using $CD34^+$ stem cell infusion in patients with GF after HID HSCT (n = 12). The median number of $CD34^+$ cells was 1.9×10^6/kg. Ten patients achieved hematopoietic recovery without serious adverse events or GVHD. Sun et al.[18] used G-PB infusion to treat patients with GF after allo-HSCT (79% were HID HSCT recipients). The median number of transfused mononuclear cells was 2.0 (1.0-5.8)$\times10^8$/kg; 53.6% of the (15/28) achieved hematopoietic recovery, and the GVHD rate was 28.6% after G-PB infusion. However, these results should be further confirmed in large multicenter studies.

3. Optimization for GVHD prophylaxis and treatment after HID HSCT

3.1 Improvement for GVHD prediction after HID HSCT

Suppressor of cytokine signaling 1 (SOCS1) is a negative regulator of several inflammatory cytokines, which could promote T-cell activation and is critical for the pathogenesis of GVHD. Guo et al.[19] observed that SOCS1 could inhibit T cell activation bythrough inhibiting the colony-stimulating factor 3 receptor/Janus kinase 2/signal transducer and activator of the transcription 3 pathway and that high expression of SOCS1 in T cells correlated with lower acute GVHD (aGVHD) occurrence after HSCT. These results suggest that SOCS1 ismight represent a potential target for attenuating GVHD.

Chang et al.[20] reported that BM allogeneic graft CD4:CD8 ratio could predict the risk of aGVHD after HID HSCT. HID HSCT recipients can be categorized into low- and high-risk groups based on this biomarker, and low-dose corticosteroid prophylaxis decreases the incidence of grade I–IV aGVHD, grade II–IV aGVHD, and moderate-to-severe chronic GVHD (cGVHD) in high-risk patients. To further integrate the risk factors for aGVHD, Shen et al.[21] established a comprehensive model (including age, sex, donor/recipient relationship, peripheral blood allogeneic graft CD3:CD14 ratio, and absolute count of CD 8^+ cells in the graft) which could predict the risk of severe aGVHD after HID HSCT.

3.2 Improvement of GVHD prophylaxis after HID HSCT

Calcineurin inhibitors (CNI; e.g., cyclosporine and tacrolimus) are among the cornerstones of GVHD prophylaxis after HID HSCT. It is generally assumed that the duration of cyclosporine

prophylaxis should be at least 6–12 months; however, considering the potential of increasing relapse and renal toxicity, some authors have tried to identify the feasibility of early tapering of CNI. In a study by Yaman et al.,[22] cyclosporine was planned for cessation starting from day 45 to day 60 after HID HSCT, and only 14 of 31 patients showed GVHD (aGVHD: 9; cGVHD: 3; overlapping GVHD: 2). However, these results should be interpreted with caution and confirmed in prospective large-cohort studies.

To further decrease the risk of GVHD, some authors have attempted to combine ATG with standard-dose PTCy (Table 3) or reduced-dose PTCy (Table 4) for GVHD prophylaxis (Table 2). In a randomized controlled trial, 122 patients were randomly assigned 1:1 to either a reduced-dose PTCy/ATG (PTCy: 80 mg/kg, ATG: 2.5 mg/kg) or a standard-dose ATG (ATG: 10 mg/kg) group. The reduced-dose PTCy/ATG group had a decreased incidence of aGVHD and improved survival compared with the standard-dose ATG group[23]. In addition, Wang et al. [24] combined rabbit ATG (10 mg/kg) with low-dose PTCy (29 mg/kg Cy) for GVHD prophylaxis in patients receiving HSCT from maternal or collateral related donors, which significantly decreased the incidence of severe aGVHD (18% vs. 5%, P = 0.003) and NRM (15% vs. 6%, P = 0.045), as well as improved the probability of GVHD-free/relapse-free survival (GRFS, 63% vs. 48%, P = 0.02) compared with those receiving ATG alone (10 mg/kg).

In addition to the combination of ATG and PTCy, Xia et al.[25] combined ATG with basiliximab for GVHD prophylaxis after HID HSCT. The 100-day cumulative incidences of grade II–IV and III–IV aGVHD were 15.8% and 5.0%, respectively, whereas the 2-year cumulative incidences of total and extensive cGVHD were 9.8% and 4.1%, respectively.

Mycophenolate mofetil (MMF) is another important component to prevent GVHD after HID HSCT. Recent studies have optimized the dose and duration of MMF prophylaxis. Elmariah et al.[26] reported that low-dose MMF (< 29 mg/kg/day) exposure was associated with an improvement in relapse and progression-free survival (PFS) without increasing the risk of GVHD compared with the high-dose group. In addition, several authors observed that patients receiving a short-term MMF prophylaxis (withdrawal till neutrophil engraftment) were associated with a decrease in Epstein□Barr virus reactivation and Epstein□Barr virus-lymphoproliferative diseases after HID HSCT compared to those receiving a long-term MMF prophylaxis (withdrawal on day 45 to 60 after transplantation) without increasing the risk of aGVDH or cGVHD, which may be

due to the improvement of the recovery of Vδ2^{+} T cells from 30 to 90 days after HID HSCT.[27, 28] Thus, this suggested that MMF prophylaxis can be withdrawn when neutrophil achieved engraftment after HID HSCT.

4. Optimization for relapse prophylaxis after HID HSCT

Several studies reported that high-risk leukemia patients benefit more from HID HSCT than MSD HSCT.[29, 30] Recently, Guo et al.[31] showed that the stronger graft-versus-leukemia activity after HID HSCT was mainly induced by decreased apoptosis and increased cytotoxic cytokine secretion, including tumor necrosis factor-α, interferon-γ, pore-forming proteins and CD107a secreted by T cells or natural killer cells. However, relapse remains a major cause of transplant failure after HID HSCT (Table 1). Currently, targeted immunotherapies to strengthen HID hold promise and have advanced to clinical therapy.

4.1 Improvement of relapse prediction after HID HSCT

Several models have been reported to predict post-transplant relapse in a specific population of HID HSCT recipients (e.g., disease risk index[11] hematopoietic cell transplantation-specific comorbidity index,[32] and disease risk comorbidity index[33]). Recently, Fan et al. developed an artificial intelligence-based predictive model (the PKU-AML model). A logistic regression model was selected as the machine learning model and five variables (AML risk category, courses of induction chemotherapy for the first complete remission, disease status, measurable residual disease [MRD] before HSCT, and blood group disparity) were included. The concordance index of the nomogram was 0.707. The Hosmer-Lemeshow test showed a good fit for this model (P = 0.205). The calibration curve was close to the ideal diagonal line, and decision curve analysis showed a significantly better net benefit in this model. The reliability of our prediction nomogram was proven in the validation cohort, independent cohort, and clinical practice. The area under the curve and average precision of this model were superior to those of other existing models for predicting post-transplant relapse after HID HSCT (J Transl Intern Med 2024, accepted).

4.2 Improvement for relapse prevention after HID HSCT

4.2.1 Prophylactic cellular therapy

The efficacy of prophylactic donor lymphocyte infusion (DLI) has been confirmed in patients with advanced-stage hematologic malignancies. Gao et al.[34] compared the outcomes of prophylactic DLI between HID and MSD HSCT recipients with identical CD3^{+} T-cell doses of DLI (2×10^{7} CD3+

cells/kg). Although HID HSCT recipients received immunosuppressants for a longer duration, the rate of grade II–IV aGVHD at 100 days was higher in the HID HSCT group than in the MSD HSCT group (59.5% vs. 30.8%, respectively). On the contrary, in a study using a lower dose of $CD3^+$ cells for prophylactic DLI,[35] that is a median dose of 0.1×10^6 $CD3^+$ T cell/kg for the first infusion and 0.5×10^6 CD3+ T cell/kg for the second infusion, the cumulative incidence of grade II–IV aGVHD at 100 days was only 17%, and the 2-year rates of relapse, NRM, and disease-free survival (DFS) was 25%, 15%, and 60%, respectively. Another multicenter study reported that haploidentical DLI with a $CD3^+$ cell count of $\geq 0.5 \times 10^6$/kg was associated with a higher rate of aGVHD.[36] Although we could not compare these results directly, it suggests that the lower dose of prophylactic DLI after HID HSCT may help to decrease the risk of severe GVHD.

Recently, a phase 2 randomized trial further identified the efficacy of donor-derived natural killer cell infusion (DNKI) after HID-HSCT in high-risk myeloid malignancy patients.[37] Donor NK cells were generated from the CD3+ cell-depleted portion of a mobilized leukapheresis product by culturing in media containing IL-15 and IL-21. The patients in the DNKI group received NK cells on days 13 (DNKI-1) and 20 (DNKI-2) after HSCT. For DNKI-1, 1×10^8 donor NK cells/kg, or approximately half of the cell culture products, were administered. For DNKI-2, the remaining cell culture products were administered. A total of 36 patients received a median DNKI dose of 1.0×10^8/kg and 1.4×10^8/kg on days 13 and 20, respectively. A lower cumulative incidence of disease progression was observed in the DNKI group (35% vs. 61%, P = 0.040), particularly in patients with primary refractory AML, refractory AML patients with < 5% peripheral blood blasts, and AML patients with normal/intermediate-risk cytogenetics. The PFS at 30 months was 33% and 11% in the DNKI and non-DNKI groups, respectively (P = 0.085). Additionally, DNKI did not increase the incidence of GF, GVHD, or infection. These encouraging results may be explained by the marked increase in memory-like NK cells after DNKI which, in turn, expands the number of $CD8^+$ effector memory T cells.

4.2.2 Preemptive interventions

Pre-emptive interventions have been widely used in MRD-positive patients. Mo et al.[38] observed that the 3-year cumulative incidences of relapse, NRM, and DFS were 35.8%, 10.7%, and 53.3%, respectively, for preemptive DLI after HID HSCT with ATG, which were comparable to those in MSD HSCT recipients. In the European Bone Marrow Transplantation report, the 2-year cumulative incidence of relapse, NRM, DFS, and OS was 61%, 17%, 22%, and 40%,

respectively, in patients receiving DLI after HID HSCT with PTCy.[35] According to the nationwide registration data of Japan which included both ATG-based and PTCy-based HID HSCT, the overall response to DLI was significantly higher in the preemptive DLI group (47.4%) than in the therapeutic group (13.9%, P = 0.002). Preemptive DLI was also a favorable factor for OS after DLI in HID HSCT recipients.[36]

For HID HSCT recipients receiving preemptive IFN-α treatments, the 2-year cumulative incidence of MRD achieving negativity and relapse was 82.8% and 15%, and the 2-year probability of leukemia-free survival (LFS) was 82.9%, respectively, which were all superior to those of MSD HSCT recipients.[39]

5. Extended application of HID HSCT in Hodgkin lymphoma

Allo-HSCT is a potentially curative strategy for the treatment of relapsed/refractory Hodgkin lymphoma. Several studies have identified the efficacy of HID HSCT with PTCy in these patients, and HID HSCT with PTCy might be associated with a lower incidence of relapse, with PFS and OS outcomes comparable to those of MSD-HSCT (Table 5). However, a report from the European Bone Marrow Transplantation database that retrospectively compared the outcomes of Hodgkin lymphoma patients receiving allo-HSCT from HLA-matched donors (96 siblings and 70 unrelated donors) and HIDs using PTCy (n = 694) showed different results. HID HSCT was associated with a higher rate of grade II-IV acute GVHD (34% vs. 24%; P = 0.01), a higher rate of NRM (18% vs. 10%; P = 0.02), and a lower rate of OS (70% vs. 82%; P = 0.002) than HLA-matched HSCT, and there were no significant differences between the two cohorts in terms of relapse, PFS, or GRFS.[40] This suggested that the efficacy of HID and MSD HSCT should be further confirmed by RCTs in HL patients.

6. Extended application of HID HSCT in elderly patients

Traditional HID HSCT conditioning regimens may lead to severe organ toxicities and a high risk of NRM, which remains a significant concern in older patients.

Recently, Sun et al. [41] established a new conditioning regimen for patients aged 55-64 years in a single-arm phase 2 study, which consisted of the following agents: cytarabine (2 g/m^2/day) on days-10 and-9; busulfan (9.6 mg/kg) from days -8 to -6; fludarabine (30 mg/m^2/day) from day -6 to day -2; cyclophosphamide (1 g/m^2/day) on days -5 and -4; semustine (250 mg/m^2) on day 3 and rabbit ATG (2.5 mg/kg/day, from days -5 to -2). The 1-year cumulative incidences of NRM and

relapse were 23.3% and 16.5%, respectively, and the 1-year probabilities of OS and LFS at 1 year were 63.5 and 60.2%, respectively. In intermediate- or high-risk AML patients aged 55□65 years, those receiving HID HSCT as consolidation therapy had a lower relapse rate (17.3% vs. 75.4%) and significantly better LFS (74.0% vs. 21.6%) than those in the chemotherapy group.

Several authors have reported that reducing the total PTCy dose to 70–80 mg/kg is a safe and valid approach for older patients with hematological malignancies receiving HID HSCT (Table 3). Fuji et al.[42] compared the outcomes of standard-dose PTCy (100 mg/kg, n = 969; median age, 57 years) and reduced-dose PTCY (80 mg/kg, n = 538; median age, 61 years) in a retrospective study. After propensity score matching, the probabilities of 2-year OS and NRM were 55.9% vs. 47.0% (P = 0.36) and 21.3% vs. 20.5% (P = 0.55) in the standard- and reduced-dose groups, respectively. The incidence of aGVHD was also compared between the groups.

A Johns Hopkins group designed non-myeloablative conditioning for HID HSCT with PTCy, including cyclophosphamide, fludarabine, and 2-Gy total body irradiation (CyFluTBI) and a BM graft.[43] The incidences of both GVHD and NRM were low, making this regimen a valuable option for older patients; however, the incidence of relapse could be as high as 46%.[11, 44] Other reduced intensity conditioning regimens based on various doses and combinations of anti-leukemic drugs (e.g. thiotepa, reduced dose busulfan, and fludarabine [TBF]), which carry more myeloablative potential and may be a more intensive alternative for AML patients who are still unfit for truly myeloablative conditioning. Recently, a retrospective multicenter compared CyFluTBI and TBF in AML complete remission (CR) patients who underwent HID HSCT with PTCy in two age-based populations. In patients ≥ 60 years, the 2-year LFS, OS, and relapse rates were 48% vs. 49% (P = 0.76), 54% vs. 55% (P = 0.84), and 22% vs. 28% (P = 0.09) for TBF and CyFluTBI, respectively; however, CyFluTBI was associated with a significantly lower risk of NRM (HR = 0.48, P = 0.03) in multivariate analysis.[45]

In addition, Bi et al.[46] reported a two-step graft engineering approach for patients ≥ 65 years old receiving HID HSCT, that is, donor lymphocytes were infused after the preparative regime, followed by cyclophosphamide to induce bidirectional tolerance, then infusion of CD34-selected cells. The 3-year OS and PFS probabilities were 36.3% and 35.6%, respectively, and the 3-year cumulative incidences of NRM and relapse were 43.5% and 21.0%, respectively, after transplantation.

Since 2016, more than 20% of the allo-HSCT recipients were aged ≥ 65 years, and 1846 patients older than 65 years received allo-HSCT in 2021 in the USA. In China, the number of allo-HSCT recipients older than 50 years will increase from 974 in 2019 to 2950 in 2021, the number of allo-HSCT recipients older than 60 years will increase from 120 in 2019 to 506 in 2021, and 67% of them will receive HID HSCT.[9]

7. Extended application of HID HSCT in patients with non-malignant hematologic disorders

7.1 HID HSCT for severe aplastic anemia

Allo-HSCT is the most important curative method for patients with severe aplastic anemia (SAA), and HID is an important alternative donor for patients with SAA without MSD. Xu et al. established a new ATG-based HID approach (i.e., busulfan 3.2 mg/kg/day on days -7 and -6; cyclophosphamide 50 mg/kg/day, from days -5 to -2, rabbit ATG 2.5 mg/kg/day, from days -5 to -2). The failure-free survival (FFS) of patients with SAA receiving HID HSCT with this approach was comparable to that of those receiving MSD HSCT for both salvage therapy (HID 86.8%, MSD 80.3%)[47] and first-line therapy (HID 86.5%, MSD 88.1%)[48]. In addition, the FFS of HID HSCT recipients was significantly better than that of those who received immunosuppressive therapy alone (83.7% vs. 38.5%), particularly in those aged < 40 years.[49]

Similarly, the BMT CTN 1502 study showed that HID bone marrow transplantation (BMT) with reduced-intensity conditioning (rabbit ATG 4.5 mg/kg in total, cyclophosphamide 14.5 mg/kg/d for 2 days, fludarabine 30 mg/m^2/d for 5 days, total body irradiation 200 cGy in a single fraction) and PTCy for GVHD prophylaxis could achieve an excellent OS (1-year OS 81%) for patients with relapsed or refractory SAA.[50] Recently, DeZern et al.[51] conducted a prospective phase 2 trial of reduced-intensity conditioning HID BMT and PTCy-based GVHD prophylaxis as initial therapy for patients with SAA. The OS of the 27 patients was 92% at 1, 2, and 3 years. In particular, HID HSCT with PTCy using 400 cGy total body irradiation resulted in 100% OS.

Severe cardiotoxicity is an early complication in patients receiving HID HSCT. Xu et al.[52] reported four adverse predictors of severe cardiotoxicity, that is, pre-transplant Eastern Cooperative Oncology Group score (≥ 2), abnormal ST-T wave on 12-lead ECG, hyperlipemia, and a recalculated cyclophosphamide dose (≥ 1.8 g/m^2/d) in the conditioning regimen. Based on this model, they developed a modified conditioning regimen including busulfan (3.2 mg/kg for 2 days), low-dose cyclophosphamide (100 mg/kg), fludarabine (150 mg/m^2), and rabbit ATG (10

mg/kg). Compared with the traditional conditioning regimen (cyclophosphamide, 200 mg/kg; busulfan, 6.4 mg/kg, and ATG, 10 mg/kg), This regimen decreased the incidence of severe cardiotoxicity (2.1% vs. 12.8%, P = 0.032). The 100-day OS and FFS probabilities were comparable between the two regimens. This optimization renders HID HSCT safer for patients with SAA.

Thus far, HID HSCT has been recommended as first-line therapy for SAA patients aged less than 50 years and a second-line option in patients aged 51-60 years in China.[53] Among patients with SAA receiving allo-HSCT, the proportion of HID has increased to more than 50% in China.[9]

7.2 HID HSCT for hereditary disease

Sickle cell disease and β-thalassemia are inherited disorders that result from genetic errors in the gene encoding β-globin. Allo-HSCT is one of the most important curative methods for these patients; however, GF is an important complication of HID HSCT. Hu et al.[54] reported that for patients with transfusion-dependent thalassemia receiving HID HSCT with PTCy, the high-dose cyclophosphamide regimen (200 mg/kg) achieved a higher incidence of stable engraftment (100% vs. 66.7%), better OS (100% vs. 88.9%), and better event-free survival (95.6% vs. 66.7%) than the low-dose cyclophosphamide regimen (120 mg/kg). Bolaños-Meade et al.[55] reported that patients with severe hemoglobinopathies who received a protocol increasing total body irradiation to 400 cGy could reduce the GF of HID BMT with PTCy. Thirteen (76%) and three (18%) of the 17 patients achieved full and mixed donor-host chimerism, respectively. All the patients were alive at their last follow-up visit.

Patients with Fanconi anemia could not tolerate intense conditioning regimens. Wang et al.[56] reported a modified HID HSCT protocol for these patients, which included 60–80 mg/kg cyclophosphamide, 150 mg/m^2 fludarabine, and 10 mg/kg rabbit ATG (n = 15). Fourteen patients survived with a median follow-up of 10.5 months, and 12 recovered with a normal blood count. The estimated 1-year DFS rate was 92.9%.

For the inherited metabolic storage diseases, particularly the lysosomal and peroxisomal storage diseases, Chen et al.[57] reported a modified HID HSCT protocol consisting of busulfan (3.2 mg/kg/day, days -8 to -6), fludarabine (30 mg/m^2/day, days -6 to -4), cyclophosphamide (50 mg/kg/day, days -5 to -2), and rabbit ATG (2.5 mg/kg/day, days -5 to -2). All six patients were alive at the last follow-up.

8. Combining with novel immunotherapy further optimized HID HSCT

8.1. Combining with new immunotherapies improves the efficacy of HID HSCT

Novel immunotherapies such as chimeric antigen receptor T (CAR-T) therapy have strong targets for hematologic malignancies, and their short-term remission is high; however, the long-term survival is unsatisfactory. Combining new immunotherapies with HID HSCT would further improve long-term clinical outcomes and allow more patients to benefit from HID HSCT (Figure 1).

8.1.1. Combining with CAR-T therapy

For relapsed/refractory ALL, pre-HSCT CAR-T therapy could help decrease the burden of the tumor and reduce the risk of post-transplant relapse. Hu et al.[58] reported the 2-year probabilities of event-free survival, OS, and relapse were 76.0%, 84.3%, and 19.7%, respectively, in patients with relapsed/refractory B-ALL who underwent bridging CAR-T therapy before HID HSCT. Zhao et al.[59] reported that HID HSCT decreased the relapse rate (17.3% vs. 67.2%) and increased the LFS rate (76.1% vs. 32.8%) in patients with relapsed/refractory B-ALL who achieved MRD negativity after CAR-T therapy.

Some studies have demonstrated the efficacy of donor-derived CAR-T therapy for relapse prophylaxis after allo-HSCT. Cheng et al.[60] reported that six patients with B-ALL (four receiving HID HSCT) with positive MRD received preemptive CAR-T therapy after allo-HSCT; five achieved MRD negativity, and three achieved long-term LFS. Zhao et al.[61] reported that 12 patients with B-ALL (66.7% receiving HID HSCT) who had positive MRD after allo-HSCT received preemptive CAR-T therapy and all achieved MRD negativity. Compared to patients who received preemptive DLI during the same period, patients receiving preemptive CAR-T had a significantly lower relapse rate and superior LFS.

In addition, Chen et al.[62] reported that six patients who experienced relapse after allo-HSCT, received donor-derived CAR-T therapy, and five achieved MRD-negative CR (83.3%); however, four patients experienced relapse again 2–7 months after CAR-T therapy. In a subsequent study with a larger sample,[63] 34 B-ALL patients (22 receiving HID HSCT) who experienced relapse after allo-HSCT received donor-derived CAR-T therapy, and 30 achieved MRD-negative CR; however, the 18-month OS rate was only 30% for those who achieved CR. During a median follow-up of 12.7 months, 17 patients experienced a relapse. Thus, the long-term survival of CAR

T remains unsatisfactory in patients with post-transplant relapse.

8.1.2. Combining with bispecific T cell engager antibodies

Blinatumomab was used in patients with relapsed/refractory B-ALL before and after HID HSCT. Wu et al.[64] reported that four patients with HLA loss relapsed after HID HSCT received blinatumomab, all achieved CR, and three achieved MRD negativity. However, in patients receiving inotuzumab ozogamicin before or after HID HSCT, attention should be paid to its specific side effects, particularly sinus obstructive syndrome, with a pooled estimated incidence of 29%.[65]

8.2. Combining with new immunotherapies improves the safety of HID HSCT.

8.2.1 Combining with virus-specific cytotoxic T cell

Cytomegalovirus (CMV) infections, particularly refractory/relapsed infections, can significantly increase the risk of NRM after HID HSCT. Zhao et al.[66] reported that treatment with CMV-specific cytotoxic T cells (CTLs) promotes the restoration of graft-derived endogenous CMV-specific immunity and effectively reduces systemic CMV infections in vivo. In addition, first-line therapy with CMV-specific CTLs promotes the quantitative and functional recovery of CTLs in patients, which is associated with CMV clearance. Recently, Pei et al.[67] reported the safety and efficacy of adoptive therapy with CMV-CTLs for CMV infections in HID HSCT recipients. The cumulative complete response rates in the first, fourth, and sixth weeks after the first CMV-CTL infusion were 37.9%, 76.8%, and 89.5%, respectively. Among patients who showed a complete response after CTL infusion, 62.7% did not experience CMV relapse during the follow-up period.

8.2.2 Combining with mesenchymal stem cells

To further decrease the risk of cGVHD, Gao et al.[68] developed a protocol using mesenchymal stem cells (MSCs) for GVHD prophylaxis after HID HSCT in a multicenter, double-blind RCT (ChiCTR-IOR-15006330). Patients were randomly chosen to receive umbilical cord-derived MSCs (MSCs group; 3×10^7 cells/100 mL/month) or normal saline (non-MSC group; 100 mL/month) for > 4 months after transplantation. The 2-year cumulative incidence of cGVHD in the MSCs group was 27.4%, which was significantly lower than that in the non-MSC group (49.0%, P = 0.021). Recently, Huang et al.[69] evaluated repeated infusions of umbilical cord MSCs during the early stage (starting 45 days after transplantation) after HID HSCT in an open-label

multicenter RCT (ChiCTR-IIR-16007806). The MSC group showed a lower incidence of severe cGVHD, grade II-IV aGVHD, and a better GRFS rate than the control group.

9. Summary and prospective

In summary, with the optimization of therapies for critical post-transplant complications, HID HSCT can be widely used in patients with hematologic malignancies or nonmalignant hematologic disorders, and HIDs have become the most important alternative donors. The rapid development of novel immunotherapies could help further improve the efficacy and safety of HID HSCT.

However, there is still room for future improvement in HID HSCT. For example, GVHD remains an important complication after HID HSCT, and clarifying the mechanism of immune tolerance after HID HSCT can help prevent GVHD. Viral infections are a major cause of transplantation failure after HID HSCT. New strategies for promoting immune reconstitution, particularly the development of universal viral CTL, could help prevent severe viral infection after HID HSCT. Lastly, new targeted drugs and cellular therapies could help patients with refractory/relapsed hematologic malignancies achieve disease remission. With the potential for long-term disease control with HID HSCT, these patients could achieve persistent DFS.

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Table 1. Major protocols for haploidentical related donor hematopoietic stem cell transplantation.

Transplant group (investigator[reference])	Conditioning regimen and GVHD prevention	Transplantation Procedures	GVHD prophylaxis after transplantation
T cell depletion			
Perugia (Aversa F[70])	Myeloablative Mega-dose CD34+ cell	8 Gy TBI, lungs shielded 4 Gy on day −9; Thiotepa (5 mg/kg daily) on days −8 and −7; Fludarabine (40 mg/m^2 daily) from day −7 to −3; ATG (5 mg/kg daily) from days −5 to −2 or ATG at a total dose of 10 mg/kg over 4 days, later reduced to 6 mg/kg	No immune suppression No G-CSF
Tuebingen (Federmann B[71])	Non-myeloablative Selective CD3/CD19 depletion	Fludarabine (150 mg/m^2 or 200 mg/m^2), Thiotepa (10 mg/kg), melphalan (120 mg/m^2); OKT-3 (5 mg/day, Days -5 to +14); fresh or cryopreserved PBSC processed with CD3/CD19 depletion on Day 0.	No G-CSF MMF (15 mg/kg bid) only if T-cell content in the graft exceeded 5×10^4 CD3$^+$ cells/kg.
Perugia (Martelli[72])	Myeloablative Tregs/Tcons protocol	Anti-T antibodies were administered 21 days before transplant. 8 Gy with lung shielding on day –10; Thiotepa (4 mg/kg daily) on days –10 and −9; Fludarabine (40 mg/m^2 daily) from days –10 to –6; Cyclophosphamide (35 mg/kg daily) on days –7 and –6; or alemtuzumab 20 mg/m^2 or ATG 3-7 mg/kg.	No
Roma (Locatelli[73])	Myeloablative TCRαβ+/CD19+ depletion	TBI (older than 3 years affected by either ALL or very high-risk AML) Anti–T-lymphocyte globulin (12 mg/kg) from day –5 to –3; rituximab (200 mg/m2) on day −1 TBI + Thiotepa + Fludarabin TBI + Thiotepa + L-PAM Thiotepa + Busulfan + Fludarabin Busulfan + Cyclophosphamide + L-PAM	No
T cell repletion			
Beijing (Huang XJ[74])	Myeloablative G-CSF+ATG based	Cytarabine (4 g/m^2 per day, on days –10 to –9), Busulfan (3.2 mg/kg per day, intravenously from days –8 to –6), Cyclophosphamide (1.8 g/m^2 per day, on days –5 to –4), Semustine (250 mg/m^2, on day –3),	Cyclosporine, mycophenolate mofetil, and short course methotrexate

		rabbit ATG (2.5mg/kg/d, from days –5 to –2,).	
Baltimore (McCurdy[11])	Non-myeloablative PTCy based	Fludarabine (30 mg/m^2 IV, from days −6 to −2, renally adjusted), Cyclophosphamide (14.5 mg/kg IV, on days −6 and −5), TBI (200 cGy, on day −1), T-cell–replete bone marrow grafting (on day 0)	High-dose PTCy (50 mg/kg IV, days +3 and +4) with mesna, mycophenolate mofetil (days 5-35), and tacrolimus (initiated day 5)

Abbreviations: GVHD, graft-versus-host disease; TBI, total-body irradiation; ATG, antithymocyte globulin; G-CSF, granulocyte colony-stimulating factor; PBSC, peripheral blood stem cell; MMF, Mycophenolate mofetil; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; L-PAM, melphalan; PTCy, post-transplant cyclophosphamide.

Table 2 Comparison between ATG-based and PTCy-based protocol in haploidentical hematopoietic stem cell transplantation

Study	Group	N	II to IV aGVHD	III to IV aGVHD	Total cGVHD	Extensive cGVHD	Relapse	NRM	DFS	OS	GRFS
Tang et al. 2020[75]	ATG	176	100-day: 26.7%	100-day: 8%	3-year: 42.3%	3-year: 9.5%	3-year: 14.9%	3-year: 12%	3-year: 74.3%	3-year: 78.3%	/
	PTCy	44	100-day: 18.2%	100-day: 6.8%	3-year: 26.2%	3-year: 5.7%	3-year: 11.7%	3-year: 27.3%	3-year: 61%	3-year: 65.2%	/
Nagler et al. 2021[76]	ATG	98	100-day: 32.7%	100-day: 11.6%	2-year: 27.7%	2-year: 7.8%	2-year: 43%	2-year: 32.9%	2-year: 24.1%	2-year: 27.4%	2-year: 20%
	PTCy	336	100-day: 30.5%	100-day: 14.1%	2-year: 31.7%	2-year: 12.1%	2-year: 33.8%	2-year: 26.7%	2-year: 39.6%	2-year: 48.4%	2-year: 31.8%
Ruggeri et al.2017[77]	ATG	115	100-day: 21%	100-day: 12.5%	2-year: 28.3%	2-year: 12.6%	2-year: 22.3%	2-year: 30.5%	2-year: 47.2%	2-year: 54.2%	2-year: 38.9%
	PTCy	193	100-day: 31%	100-day: 4.7%	2-year: 33.7%	2-year: 8.6%	2-year: 21.6%	2-year: 22.4%	2-year: 56%	2-year: 58%	2-year: 50.9%
Bazarbachi et al.2024[78]	ATG	358	180-day: 27.5%	180-day: 11.6%	2-year: 30.5%	2-year: 11%	NA*	NA	NA	NA	NA
	PYCy	2999	180-day: 30.4%	180-day: 9.6%	2-year: 31.4%	2-year: 11.3%	NA	NA	NA	NA	NA

Abbreviations: aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; NRM, non-relapse mortality; DFS, disease-free survival; OS, overall survival; GRFS, GVHD-free/relapse-free survival; NA, not applicable; ATG, anti□thymocyte globulin; PTCy, posttransplant cyclophosphamide

*Compared to PTCy, ATG had a higher risk of NRM (HR, 1.6; $P = 0.003$), worse LFS (HR, 1.4; $P = 0.002$), OS (HR, 1.49; $P = 0.0009$), and GRFS (HR, 1.29; $P = 0.012$).

Table 3. Combination of standard-dose of PTCy with ATG in haploidentical related donor hematopoietic stem cell transplantation.

Study	Disease	PTCy and ATG total doses	N	Grade 2–4 aGvHD	cGvHD	Relapse	NRM	GRFS	OS
Dulery et al. 2018[79]	R/R HM	PTCy 100 mg/kg + ATG-T 5 mg/kg	27	11% at 100 days	30% at 2 years	30% at 2 years	15% at 2 years	44% at 2 years	55% at 2 years
Dulery et al. 2019[80]	HM	PTCy 50mg/kg or 100 mg/kg + ATG 2.5 or 5 mg/kg	39	21% at 100 days	25% at 2 years	22% at 2 years	18% at 2 years	NA	71% at 2 years
Salas et al. 2019[81]	AML, MDS, MPN	PTCy 100 mg/kg + ATG-T 4.5mg/kg	47	17% at 100 days	17% at 2 years	13% at 1 year	37% at 1 year	NA	54% at 1 year
Peric et al. 2020[82]	HM	PTCy 100 mg/kg + ATG-T 5 or 10 mg/kg	80	30% at 180 days	32% at 2 years	26% at 2 years	26% at 2 years	NA	53% at 2 years
El-Cheikh et al. 2020[83]	HM	PTCy 100 mg/kg + ATG-T 2.5 to 5 mg/kg	69	12% at 1 year	23% at 1 year	25% at 1 year	8% at 1 year	45% at 1 year	79% at 1 year
Salas et al. 2021[84]	HM	PTCy 100 mg/kg + ATG-T 4.5 mg/kg PTCy 100 mg/kg + ATG-T 2 mg/kg	60 35	22.3% at 100 days	20% at 1 year	17% at 1 year	36% at 1 year	31% at 1 year	51% at 1 year
Xue et al. 2022[85]	HM	PTCy 100 mg/kg + ATG-F 5 mg/kg	21	24% at 100 days	15% at 1 year	25% at 1 year	19% at 1 year	NA	75% at 1 year

Abbreviations: PTCy, posttransplant cyclophosphamide; ATG, anti□thymocyte globulin; N, number of patients; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; NRM, non-relapse mortality; GRFS, GvHD-free, relapse-free survival; OS, overall survival; R/R, relapsed/refractory; HM, hematological malignancies; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; ATG-T, anti-thymocyte globulin (thymoglobuline); ATG-F, anti-thymocyte globulin (ATG Fresenius/Neovii); NA, not available.

Table 4. Combination of reduced-dose PTCy and/or ATG in haploidentical related donor hematopoietic stem cell transplantation.

Study	Disease	Low-dose PTCY±ATG alone/ versus Standard-dose PTCY±ATG	N	Grade 2–4 aGvHD	cGvHD	Relapse	NRM	GRFS	OS
Barkhordar et al. 2022[86]	AML	PTCY 80 mg/kg + ATG-T 7.5 mg/kg	92	27% at 100 days	15% at 1 year	16% At 5 years	29% at 5 years	44%	58%
Zhou et al. 2022[87]	HM	PTCY 50 mg/kg + ATG-T 5 mg/kg	90	12% at 100 days	31% at 1 year	Low ALC 33% High ALC 12% at 1 year	Low ALC 19% High ALC 13% at 1 year	Low ALC 43% High ALC 65% at 1 year	Low ALC 52% High ALC 79% at 1 year
Dulery et al. 2023[88]	HM (Age>65 years)	PTCY 80 mg/kg + ATG 2.5 to 5 mg/kg versus	38	32% at 180 days	41% at 2 years	19% at 2 years	16% at 2 years	52% at 2 years	70% at 2 years
		PTCY 100 mg/kg + ATG 2.5 to 5 mg/kg	55	33% at 180 days	35% at 2 years	20% at 2 years	31% at 2 years	36% at 2 years	56% at 2 years
Zhang et al. 2023[23]	HM	PTCY 80mg/kg + ATG 2.5 mg/kg versus	61	11.5% at 100 days	24.2% at 2 years	11.1% at 2 years	16.2% at 2 years	61.3% at 2 years	75.4% at 2 years
		ATG 10mg/kg	61	39.3%** at 100 days	39.9% at 2 years	16.2% at 2 years	28.8% at 2 years	42.3%* at 2 years	54.1%* at 2 years
Dulery et al. 2023[89]	HM (Age≥65 years)	PTCY 70mg/kg + ATG 2.5mg/kg versus	33	18% at 180 days	27% at 2 years	30% at 2 years	18% at 2 years	60% at 2 years	68% at 2 years
		PTCy 100 mg/kg + ATG 5.0 mg/kg	25	17% at 180 days	29% at 2 years	21% at 2 years	33% at 2 years	33%* at 2 years	52% at 2 years
Fuji et al. 2024[42]	HM	PTCY 80 mg/kg versus	425	25.3%, 29.2%	28.8% 24.4%	33.3% 28.7%	20.5% 21.3%	38.0% 40.9%	47.0% 55.9%
		PTCY 100 mg/kg	425	at 100 days	at 2 years	at 2 years	at 2 years	at 2 years	at 2 years

Abbreviations: PTCy, posttransplant cyclophosphamide; ATG, anti□thymocyte globulin; N, number of patients; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; NRM, non-relapse mortality; GRFS, GvHD-free, relapse-free survival; OS, overall survival; AML, acute myeloid leukemia; HM, hematological malignancies; NA, not available.*: $P < 0.05$; **: $P < 0.01$.

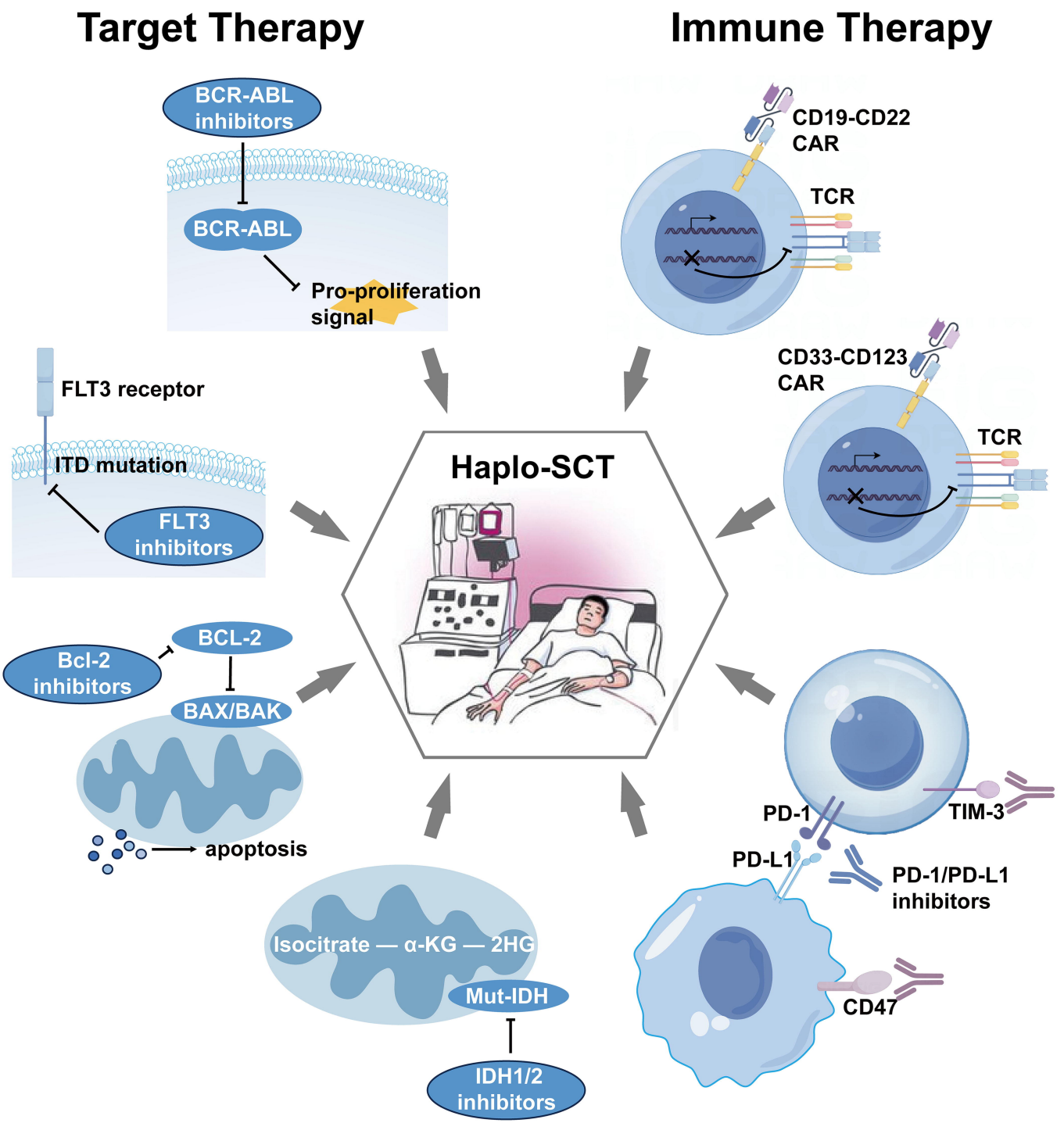
Table 5. Haploidentical related donor HSCT for Hodgkin's lymphoma.

Study	Donor Type	N	Prior ASCT	PTCy doses	Grade 2–4 aGvHD	cGvHD	Relapse	NRM	GRFS	OS
Raiola et al. 2014[90]	HID	26	26	PTCy 100mg/kg	24% at 100d	9% at 3y	31% at 18m	4% at 4y	(PFS)63% at 4y	77% at 4y
Martínez et al. 2017[91]	HID	98	75	PTCy NA	33%**	26%* at 1y	39%* at 2y	17%** at 1y	NA	67%* at 2y
	MSD	338	236		18%**	25%* at 1y	49%*,** at 2y	13% at 1y	NA	71% at 2y
	MUD	273	206		30%	41%*,* at 1y	32%**	21%** at 1y	NA	62%* at 2y
Marani et al. 2018[92]	HID	41	40	PTCy 100 mg/kg	20.7% at 100d	11.8% at 3y	7.5% at 3y	55.4% at 3y	39% at 3y	75.6% at 3y
Gauthier et al. 2018[93]	HID	61	53	PTCy 100 mg/kg	29% at 100d	15% at 2y	21% at 2y	9% at 2y	58% at 2y	81% at 2y
	MSD	90	80	ATG 2.5 to 5 mg/kg	22% at 100d	37% at 2y*	15% at 2y	12% at 2y	42% at 2y*	82% at 2y
Mariotti et al. 2018[94]	HID	30	30	PTCy 100mg/kg	23% at 1y	3% at 2y	13% at 3y	26% at 1y	17% at 1y	56% at 3y
	MSD	34	34		29% at 1y	32% at 2y**	62% at 3y**	9% at 1y	47% at 1y	52% at 3y
Ahmed et al. 2019[95]	HID	139	102	PTCy NA	45% at 180d	23% at 1y	32% at 1y	11% at 1y	NA	78% at 1y 63% at 3y
	MSD	457	382		30% at 180d**	46% at 1y**	42% at 1y*	6% at 1 y	NA	84% at 1y 63% at 3y
Montoro et al. 2024[40]	HID	694	520	PTCy NA	34% at 100d	27% at 2y	22% at 2y	18% at 2y	51% at 2y	70% at 2y
	MSD, MUD	96,70	106		24% at 100d**	26% at 2y	24% at 2y	10% at 2y*	55% at 2y	82% ay 2y**

Abbreviations: N, number of patients; ASCT, autologous stem cell transplantation; PTCy, post-transplant cyclophosphamide; NRM, non-relapse mortality; GRFS, GvHD-free, relapse-free survival; OS, overall survival; ATG, anti-thymocyte globulin; MSD, matched sibling donors; MUD, matched unrelated donors; HID, haploidentical donors; PFS, progression-Free Survival; NA, not available.*: $P < 0.05$; **: $P < 0.01$.

Figure Legend

Figure 1. Targeted and Immune Therapies Enhance Haploidentical Hematopoietic Stem Cell Transplantation. HID HSCT could clear the tumor cells through different mechanisms, such as the direct killing effects of conditioning regimen and the graft-versus-tumor effect, and it is still the important curative method for most of the hematologic malignancies. By incorporating novel immunotherapies, such as targeted agents (e.g., BCR-ABL, FLT3, IDH1/IDH2, and BCL-2 inhibitors) and immune-based therapies (e.g., CAR-T, PD-1/PD-L1, and TIM3 inhibitors), HID HSCT has the potential to significantly improve long-term clinical outcomes, enabling more patients to benefit from this approach. Abbreviations: HID, haploidentical donors; HSCT, hematopoietic stem cell transplantation; BCR-ABL, breakpoint cluster region-abelson; FLT3, Fms-like tyrosine kinase 3; I IDH1/IDH2, isocitrate dehydrogenase 1/2; BCL-2, B-cell Lymphoma 2 inhibitors; CAR-T, chimeric antigen receptor T-cell; PD-1, programmed death-1/programmed death-ligand 1; TIM3, T-cell immunoglobulin and mucin-domain containing-3.


Target Therapy
Immune Therapy
BCR-ABL inhibitors
BCR-ABL
Pro-proliferation signal
CD19-CD22 CAR
TCR
FLT3 receptor
ITD mutation
FLT3 inhibitors
CD33-CD123 CAR
TCR
Haplo-SCT
Bcl-2 inhibitors
BCL-2
BAX/BAK
apoptosis
PD-1
TIM-3
PD-L1
PD-1/PD-L1 inhibitors
Isocitrate — α-KG — 2HG
Mut-IDH
IDH1/2 inhibitors
CD47