REVIEW ARTICLE

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

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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. Combining this approach with novel immunotherapy could further improve the efficacy and safety of HID HSCT. This review focuses on recent progress in the optimization of HID HSCT.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is one of the most important curative methods for hematologic malignancies.[1,2] A human leukocyte antigen (HLA)-matched sibling donor (MSD) is the first choice for allogeneic 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. Given 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),[3-8] the high incidence of graft rejection and relapse significantly affected the survival of HID HSCT recipients.

Based on the immune tolerance induced by 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 since the optimization of major transplant techniques. Several multicenter prospective studies confirmed that the clinical outcomes of HID HSCT recipients following this protocol were significantly better than those who received chemotherapies as consolidation in acute myeloid leukemia (AML)[9] or acute lymphoblastic leukemia (ALL),[10] which were similar to those who received MSD HSCT.[11-13] Currently, the Beijing protocol is used for over 90% of HID HSCT in China, and HID HSCT accounted for 63% (7,977/31,525) of allogeneic HSCT in 2019 compared to 29.6% (313/1,062) in 2008 according to data from the Chinese Blood and Marrow Transplantation Registry Group.[14,15]

In addition, colleagues at Johns Hopkins University proposed a modality with T-cell-replete and 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%,[8,16] respectively, for HID HSCT following this protocol (Table 1).[3-8] 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).[17-20]

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

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

Transplant group (investigator)	Conditioning regimen and GvHD prevention	Transplantation procedures	GvHD prophylaxis after transplantation
T-cell depletion			
Perugia (Aversa F[3])	Myeloablative Mega-dose $CD34^+$ cells	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[4])	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[5])	Myeloablative Treg/Tcon 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[6])	Myeloablative TCR$\alpha\beta^+$/$CD19^+$ depletion	TBI (older than 3 years affected by either ALL or very high-risk AML). Anti-T-lymphocyte globulin (12 mg/kg) from days –5 to –3; Rituximab (200 mg/m^2) on day –1 TBI + thiotepa + fludarabine TBI + thiotepa + L-PAM Thiotepa + busulfan + fludarabine Busulfan + cyclophosphamide + L-PAM.	No
T-cell-replete			
Beijing (Huang XJ[7])	Myeloablative G-CSF + ATG-based	Cytarabine (4 g/m^2 per day, on days –10 and –9); Busulfan (3.2 mg/kg per day, IV from days –8 to –6); Cyclophosphamide (1.8 g/m^2 per day, on days –5 and –4); Semustine (250 mg/m^2, on day –3); rabbit ATG (2.5 mg/kg/day, from days –5 to –2).	Cyclosporine, MMF, and short-course methotrexate
Baltimore (McCurdy[8])	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, MMF (days 5-35), and tacrolimus (initiated day 5)

GvHD: graft-*versus*-host disease; TBI: total-body irradiation; ATG: antithymocyte globulin; G-CSF: granulocyte colony-stimulating factor; PBSC: peripheral blood stem cells; MMF: mycophenolate mofetil; Treg/Tcon: regulatory T cells/conventional effector T cells; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; L-PAM: melphalan; IV: intravenous; PTCy: post-transplant cyclophosphamide.

Optimization of hematopoietic reconstitution after haploidentical hematopoietic stem cell transplantation

With the increasing use of HID HSCT, poor graft function, defined as a hypoplastic or aplastic bone marrow with two or three of the following: (i) neutrophil count ≤0.5×10^9/L; (ii) platelet count ≤20×10^9/L; and/or (iii) hemoglobin concentration ≤70 g/L for at least 3 consecutive days after day +28 following the HSCT or in accordance with platelet 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 poor graft function is 4-5% after HID HSCT;[21] however, it can seriously influence the quality of life and increase the risk of non-relapse mortality.

New pathogenesis-oriented approaches for poor hematopoietic function after haploidentical hematopoietic stem cell transplantation

The bone marrow microenvironment is critical for the regulation of hematopoietic stem cells, and endothelial cells play essential roles in regulating hematopoiesis.[22] Kong *et al.*[23] demonstrated that defective bone marrow endothelial cells before HSCT and impaired bone marrow endothelial

Table 2. Comparison between antithymocyte globulin-based and post-transplant cyclophosphamide-based protocols in haploidentical hematopoietic stem cell transplantation.

Study	Group	N	Grade 2-4 acute GvHD	Grade 3-4 acute GvHD	Total chronic GvHD	Extensive chronic GvHD	Relapse	NRM	DFS	OS	GRFS
Tang *et al.* 2020[17]	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[18]	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[19]	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[20]	ATG	358	180-day 27.5%:	180-day: 11.6%	2-year: 30.5%	2-year: 11%	NA*	NA	NA	NA	NA
	PYCy	2,999	180-day: 30.4%	180-day: 9.6%	2-year: 31.4%	2-year: 11.3%	NA	NA	NA	NA	NA

*Compared to patients treated with post-transplant cyclophosphamide, those given an antithymocyte globulin-based protocol had a higher risk of non-relapse mortality (hazard ratio [HR]=1.6; *P*=0.003), worse leukemia-free survival (HR=1.4; *P*=0.002), overall survival (HR=1.49; *P*=0.0009), and GRFS (HR=1.29; *P*=0.012). GvHD: graft-*versus*-host disease; NRM: non-relapse mortality; DFS: disease-free survival; OS: overall survival; GRFS GvHD-free/relapse-free survival; ATG: antithymocyte; PTCy: post-transplant cyclophosphamide; NA: not applicable.

cell reconstitution at early time points after HSCT were positively correlated with levels of reactive oxygen species, and bone marrow endothelial cells <0.1% before HSCT could identify high-risk patients with poor graft function after HID HSCT. In a randomized controlled trial,[24] HID HSCT recipients with bone marrow endothelial cells <0.1% were randomly assigned to a group given N-acetyl-L-cysteine prophylaxis or a group not given such prophylaxis. N-acetyl-L-cysteine prophylaxis improved bone marrow endothelial cells and $CD34^+$ cells, reduced levels of reactive oxygen species after HSCT, and decreased the incidence of poor graft function after HID HSCT in high-risk patients. We should emphasize that endothelial cell dysfunction and reactive oxygen species represent just two of several components contributing to the complex pathogenesis of poor graft function.

Cellular therapies for graft failure after haploidentical hematopoietic stem cell transplantation

Secondary transplantation is the most intensive salvage cellular therapy for severe graft failure. 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 a combination of G-CSF-primed bone marrow and G-CSF-mobilized peripheral blood stem cell 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 (60.0% *vs*. 26.4%, *P*=0.011) were better in the novel regimen group.[25]

Other cellular therapies for the treatment of graft failure after HID HSCT have also been reported. Fei *et al*.[26] using $CD34^+$ stem cell infusion in patients with graft failure 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*.[27] used infusion of G-CSF-mobilized peripheral blood stem cells to treat patients with graft failure after allogeneic HSCT (79% were HID HSCT recipients). The median number of transfused mononuclear cells was 2.0 (1.0-5.8)×10^8/kg; 53.6% of the 15/28 transplanted patients achieved hematopoietic recovery, and the GvHD rate was 28.6% after G-CSF-mobilized peripheral blood stem cell infusion. However, these results should be further confirmed in large multicenter studies.

Optimization of graft-*versus*-host disease prophylaxis and treatment after haploidentical hematopoietic stem cell transplantation

Improvement of graft-*versus*-host disease prediction after haploidentical hematopoietic stem cell transplantation

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*.[28] observed that SOCS1 could inhibit T-cell activation by 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 less occurrence of acute GvHD after HSCT. These results suggest that SOCS1 might represent a potential target for attenuating GvHD.

Chang *et al.*[29] reported that bone marrow allogeneic graft CD4:CD8 cell ratio could predict the risk of acute GvHD 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 acute GvHD, grade II-IV acute GvHD, and moderate-to-severe chronic GvHD in high-risk patients. To further integrate the risk factors for acute GvHD, Shen *et al.*[30] established a comprehensive model (including age, sex, donor/recipient relationship, peripheral blood allogeneic graft CD3:CD14 cell ratio, and absolute count of $CD8^+$ cells in the graft) which could predict the risk of severe acute GvHD after HID HSCT.

Improvement of graft-*versus*-host disease prophylaxis after haploidentical hematopoietic stem cell transplantation

Calcineurin inhibitors (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 calcineurin inhibitors. In a study by Yaman *et al.*,[31] cyclosporine was planned for cessation starting from day 45 to day 60 after HID HSCT, and only 14 of 31 patients developed GvHD (acute GvHD: 9; chronic GvHD: 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)[32-38] or reduced-dose PTCy (Table 4)[39-44] for GvHD prophylaxis (Table 2).[17-20] 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 acute GvHD and improved survival compared with the standard-dose ATG group.[42] In addition, Wang *et al.*[45] combined rabbit ATG (10 mg/kg) with low-dose PTCy (29 mg/kg) for GvHD prophylaxis in patients receiving HSCT from maternal or collateral related donors, which significantly decreased the incidence of severe acute GvHD (18% *vs.* 5%, P=0.003) and non-relapse mortality (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.*[46] combined ATG with basiliximab for GvHD prophylaxis after HID HSCT. The 100-day cumulative incidences of grade II-IV and III-IV acute GvHD were 15.8% and 5.0%, respectively, whereas the 2-year cumulative incidences of total and extensive chronic GvHD were 9.8% and 4.1%, respectively.

Mycophenolate mofetil is another important component to prevent GvHD after HID HSCT. Recent studies have optimized the dose and duration of mycophenolate mofetil prophylaxis. Elmariah *et al.*[47] reported that low-dose mycophenolate mofetil (<29 mg/kg/day) exposure was associated with an improvement in relapse and progression-free survival without

Table 3. Combination of standard-dose post-transplant cyclophosphamide with antithymocyte globulin in haploidentical-related donor hematopoietic stem cell transplantation.

Study	Disease	PTCy and ATG total doses	N	Grade 2-4 acute GvHD	Chronic GvHD	Relapse	NRM	GRFS	OS
Dulery *et al.* 2018[32]	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[33]	HM	PTCy 50 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[34]	AML, MDS, MPN	PTCy 100 mg/kg + ATG-T 4.5 mg/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[35]	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[36]	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[37]	HM	PTCy 100 mg/kg + ATG-T 4.5 mg/kg	60	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
		PTCy 100 mg/kg + ATG-T 2 mg/kg	35						
Xue *et al.* 2022[38]	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

PTCy: post-transplant cyclophosphamide; ATG: antithymocyte globulin; N: number of patients; GvHD: graft-*versus*-host disease; NRM: non-relapse mortality; GRFS: GvHD-free, relapse-free survival; OS: overall survival; R/R: relapsed/refractory; HM: hematologic 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.

increasing the risk of GvHD compared with the outcomes of the high-dose group. In addition, several authors observed that patients receiving a short course of mycophenolate mofetil prophylaxis (withdrawal with neutrophil engraftment) had a decrease in Epstein-Barr virus reactivation and Epstein-Barr virus-lymphoproliferative diseases after HID HSCT compared to patients who received long-term mycophenolate mofetil prophylaxis (withdrawal on day 45-60 after transplantation) without increasing the risk of acute or chronic GvHD, which may be due to the improvement of the recovery of Vδ2$^+$ T cells from 30 to 90 days after HID HSCT.[48,49] Thus, this suggested that prophylaxis with mycophenolate mofetil can be withdrawn when neutrophil engraftment is achieved after HID HSCT.

Optimization of relapse prophylaxis after haploidentical hematopoietic stem cell transplantation

Several studies reported that high-risk leukemia patients benefit more from HID HSCT than from MSD HSCT.[50,51] Recently, Guo *et al.*[52] 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 (NK) cells. However, relapse remains a major cause of transplant failure after HID HSCT (Table 1).[3-8] Currently, targeted immunotherapies to strengthen HID hold promise and have advanced to clinical therapy.

Improvement of relapse prediction after haploidentical hematopoietic stem cell transplantation

Several models have been reported to predict post-transplant relapse in a specific population of HID HSCT recipients (e.g., disease risk index,[8] hematopoietic cell transplantation-specific comorbidity index,[53] and disease risk comorbidity index[54]). Recently, Fan *et al.* developed an artificial intelligence-based predictive model (the PKU-AML model).[55] A logistic regression model was selected as the machine learning model and five variables (AML risk

Table 4. Combination of reduced-dose post-transplant cyclophosphamide and/or antithymocyte globulin in haploidentical-related donor hematopoietic stem cell transplantation.

Study	Disease	Low-dose PTCy±ATG alone *versus* standard-dose PTCy±ATG	N	Grade 2-4 acute GvHD	Chronic GvHD	Relapse	NRM	GRFS	OS
Barkhordar *et al.* 2022[39]	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[40]	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[41]	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[42]	HM	PTCy 80 mg/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 10 mg/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[43]	HM (Age ≥65 years)	PTCy 70 mg/kg + ATG 2.5 mg/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[44]	HM	PTCy 80 mg/kg *versus*	425	25.3% at 100 days	28.8% at 2 years	33.3% at 2 years	20.5% at 2 years	38.0% at 2 years	47.0% at 2 years
		PTCy 100 mg/kg	425	29.2% at 100 days	24.4% at 2 years	28.7% at 2 years	21.3% at 2 years	40.9% at 2 years	55.9% at 2 years

PTCy: post-transplant cyclophosphamide; ATG: antithymocyte globulin; N: number of patients; GvHD: graft-*versus*-host disease; NRM: non-relapse mortality; GRFS: GvHD-free, relapse-free survival; OS: overall survival; AML: acute myeloid leukemia; HM: hematologic malignancies; ALC: absolute lymphocyte count; *P<0.05; **P<0.01.

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, an 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[55].

Improvement of relapse prevention after haploidentical hematopoietic stem cell transplantation

Prophylactic cellular therapy

The efficacy of prophylactic donor lymphocyte infusion (DLI) has been confirmed in patients with advanced-stage hematologic malignancies. Gao *et al.*[56] 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 acute GvHD 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,[57] that is, a median dose of 0.1×10^6 $CD3^+$ T cells/kg for the first infusion and 0.5×10^6 $CD3^+$ T cells/kg for the second infusion, the cumulative incidence of grade II-IV acute GvHD at 100 days was only 17%, and the 2-year rates of relapse, non-relapse mortality, and disease-free survival were 25%, 15%, and 60%, respectively. Another multicenter study found that haploidentical DLI with a $CD3^+$ cell count of $\geq0.5\times10^6$/kg was associated with a higher rate of acute GvHD.[58] 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 II randomized trial further identified the efficacy of donor-derived natural killer cell infusion (DNKI) after HID-HSCT in high-risk myeloid malignancy patients.[59] Donor NK cells were generated from the $CD3^+$ cell-depleted portion of a mobilized leukapheresis product by culturing in media containing interleukin-15 and interleukin-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 progression-free survival 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 graft failure, 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.

Pre-emptive interventions

Pre-emptive interventions have been widely used in MRD-positive patients. Mo *et al.*[60] observed that the 3-year cumulative incidences of relapse, non-relapse mortality, and disease-free survival were 35.8%, 10.7%, and 53.3%, respectively, for pre-emptive 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, non-relapse mortality, disease-free survival, and overall survival were 61%, 17%, 22%, and 40%, respectively, in patients receiving DLI after HID HSCT with PTCy.[57] According to nationwide registry data from Japan, which included both ATG-based and PTCy-based HID HSCT, the overall response to DLI was significantly higher in the group given pre-emptive DLI (47.4%) than in the therapeutic group (13.9%, *P*=0.002). Pre-emptive DLI was also a favorable factor for overall survival after DLI in HID HSCT recipients.[58]

For HID HSCT recipients receiving pre-emptive treatment with interferon-α, the 2-year cumulative incidence of patients with MRD achieving negativity and relapse was 82.8% and 15%, and the 2-year probability of leukemia-free survival was 82.9%, which were all superior to those of MSD HSCT recipients.[61]

Extended application of haploidentical hematopoietic stem cell transplantation in Hodgkin lymphoma

Allogeneic 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 progression-free survival and overall survival outcomes comparable to those of MSD HSCT (Table 5).[62-67] However, a report from the European Bone Marrow Transplantation database that retrospectively compared the outcomes of Hodgkin lymphoma patients receiving allogeneic HSCT from HLA-matched donors (96 siblings and 70 unrelated donors) and HID 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 non-relapse

Table 5. Haploidentical-related donor hematopoietic stem cell transplantation for Hodgkin lymphoma.

Study	Donor type	N	Prior ASCT	PTCy doses	Grade 2-4 acute GvHD	Chronic GvHD	Relapse	NRM	GRFS	OS
Raiola *et al.* 2014[62]	HID	26	26	PTCy 100 mg/kg	24% at 100 days	9% at 3 y	31% at 18 months	4% at 4 y	(PFS) 63% at 4 y	77% at 4 y
Martínez *et al.* 2017[63]	HID	98	75	PTCy NA	33%**	26%* at 1 y	39%* at 2 y	17%** at 1 y	NA	67%* at 2 y
Marani *et al.* 2018[64]	MSD	338	236	PTCy 100 mg/kg	18%**	25%* at 1 y	49%*,** at 2 y	13% at 1 y	NA	71% at 2 y
	MUD	273	206		30%	41%** at 1 y	32%**	21%** at 1y	NA	62%* at 2 y
	HID	41	40		20.7% at 100 days	11.8% at 3 y	7.5% at 3 y	55.4% at 3 y	39% at 3 y	75.6% at 3 y
Gauthier *et al.* 2018[65]	HID	61	53	PTCy 100 mg/kg	29% at 100 days	15% at 2 y	21% at 2 y	9% at 2 y	58% at 2 y	81% at 2 y
	MSD	90	80	ATG 2.5 to 5 mg/kg	22% at 100 days	37% at 2 y*	15% at 2 y	12% at 2 y	42% at 2 y*	82% at 2 y
Mariotti *et al.* 2018[66]	HID	30	30	PTCy 100 mg/kg	23% at 1 year	3% at 2 y	13% at 3 y	26% at 1y	17% at 1 y	56% at 3 y
	MSD	34	34		29% at 1 year	32% at 2 y**	62% at 3 y**	9% at 1y	47% at 1 y	52% at 3 y
Ahmed *et al.* 2019[67]	HID	139	102	PTCy NA	45% at 180 days	23% at 1 y	32% at 1 y	11% at 1 y	NA	78% at 1 y 63% at 3 y
	MSD	457	382		30% at 180 days**	46% at 1 y**	42% at 1 y*	6% at 1 y	NA	84% at 1 y 63% at 3 y
Montoro *et al.* 2024[68]	HID	694	520	PTCy NA	34% at 100 days	27% at 2 y	22% at 2 y	18% at 2 y	51% at 2 y	70% at 2 y
	MSD, MUD	96, 70	106		24% at 100 days**	26% at 2 y	24% at 2 y	10% at 2 y*	55% at 2 y	82% at 2 y**

N: number of patients; ASCT: autologous stem cell transplantation; PTCy: post-transplant cyclophosphamide; GvHD: graft-versus-host disease-free; NRM: non-relapse mortality; GRFS: GvHD-free, relapse-free survival; OS: overall survival; HID: haploidentical donors; y: year(s); PFS: progression-free survival; NA: not available; MSD: matched sibling donors; MUD: matched unrelated donors; ATG: antithymocyte globulin. *P<0.05; **P<0.01.

mortality (18% *vs*. 10%; P=0.02), and a lower rate of overall survival (70% *vs*. 82%; P=0.002) than HLA-matched HSCT, and there were no significant differences between the two cohorts in terms of relapse, progression-free survival, or GRFS.[68] This suggested that the efficacy of HID and MSD HSCT should be further confirmed by randomized controlled trials in patients with Hodgkin lymphoma.

Extended application of haploidentical hematopoietic stem cell transplantation in elderly patients

Traditional HID HSCT conditioning regimens may lead to severe toxicity to organs and a high risk of non-relapse mortality, which remains a significant concern in older patients.

Recently, Sun *et al.*[69] established a new conditioning regimen for patients aged 55-64 years in a single-arm phase II 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 non-relapse mortality and relapse were 23.3% and 16.5%, respectively, and the 1-year probabilities of overall survival and leukemia-free survival 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 leukemia-free survival (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 hematologic malignancies receiving HID HSCT (Table 3).[32-38] Fuji *et al.*[44] 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 overall survival and non-relapse mortality 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 acute GvHD was also compared between the groups.

A Johns Hopkins group designed non-myeloablative con-

ditioning for HID HSCT with PTCy, including cyclophosphamide, fludarabine, and 2-Gy total body irradiation (CyFluTBI) and a bone marrow graft.[70] The incidences of both GvHD and non-relapse mortality were low, making this regimen a valuable option for older patients; however, the incidence of relapse could be as high as 46%.[8,71] Other reduced intensity conditioning regimens based on various doses and combinations of antileukemic 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 patients in complete remission who underwent HID HSCT with PTCy in two age-based populations. In patients ≥60 years, the 2-year leukemia-free survival, overall survival, 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 non-relapse mortality (hazard ratio=0.48, P=0.03) in multivariate analysis.[72] In addition, Bi *et al*.[73] 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 overall and progression-free survival probabilities were 36.3% and 35.6%, respectively, and the 3-year cumulative incidences of non-relapse mortality and relapse were 43.5% and 21.0%, respectively, after transplantation.

Since 2016, more than 20% of the allogeneic HSCT recipients were aged ≥65 years, and 1,846 patients older than 65 years received allogeneic HSCT in 2021 in the USA. In China, the number of allogeneic HSCT recipients older than 50 years increased from 974 in 2019 to 2,950 in 2021, the number of allogeneic HSCT recipients older than 60 years increased from 120 in 2019 to 506 in 2021, and 67% of them received HID HSCT.[15]

Extended application of haploidentical hematopoietic stem cell transplantation in patients with non-malignant hematologic disorders

Haploidentical hematopoietic stem cell transplantation for severe aplastic anemia

Allogeneic HSCT is the most important curative method for patients with severe aplastic anemia, and HID are important alternative donors for patients with severe aplastic anemia 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 of patients with severe aplastic anemia 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%)[74] and first-line therapy (HID 86.5%, MSD 88.1%).[75] In addition, the failure-free survival 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.[76]

Similarly, the BMT CTN 1502 study showed that HID bone marrow transplantation with reduced-intensity conditioning (rabbit ATG 4.5 mg/kg in total, cyclophosphamide 14.5 mg/kg/day for 2 days, fludarabine 30 mg/m^2/day for 5 days, total body irradiation 200 cGy in a single fraction) and PTCy for GvHD prophylaxis could achieve an excellent overall survival (1-year overall survival, 81%) for patients with relapsed or refractory severe aplastic anemia.[77] Recently, DeZern *et al*.[78] conducted a prospective phase II trial of reduced-intensity conditioning HID bone marrow transplantation and PTCy-based GvHD prophylaxis as initial therapy for patients with severe aplastic anemia. The overall survival 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% overall survival.

Severe cardiotoxicity is an early complication in patients receiving HID HSCT. Xu *et al*.[79] reported four adverse predictors of severe cardiotoxicity, that is, pre-transplant Eastern Cooperative Oncology Group score (≥2), abnormal ST-T waves on 12-lead electrocardiography, hyperlipidemia, and a recalculated cyclophosphamide dose (≥1.8 g/m^2/day) 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 overall survival and failure-free survival probabilities were comparable between the two regimens. This optimization renders HID HSCT safer for patients with severe aplastic anemia.

Thus far, HID HSCT has been recommended as first-line therapy for patients with severe aplastic anemia aged less than 50 years and a second-line option in patients aged 51-60 years in China.[80] Among patients with severe aplastic anemia receiving allogeneic HSCT, the proportion of HID has increased to more than 50% in China.[15]

Haploidentical hematopoietic stem cell transplantation for hereditary diseases

Sickle cell disease and β-thalassemia are inherited disorders that result from genetic errors in the gene encoding β-globin. Allogeneic HSCT is one of the most important curative methods for patients with these disorders; however, graft failure is an important complication of HID HSCT. Hu *et al*.[81] 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 overall survival (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*.[82] reported that patients with severe hemoglobinopathies who received a protocol in which total body irradiation was increased to 400 cGy hsd a reduction of graft failure of HID bone marrow transplantation 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 may not tolerate intense conditioning regimens. Wang *et al*.[83] 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 disease-free survival rate was 92.9%.

For the inherited metabolic storage diseases, particularly lysosomal and peroxisomal storage diseases, Chen *et al*.[84] 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.

Combination with novel immunotherapy further optimizes haploidentical hematopoietic stem cell transplantation

Combination with new immunotherapies improves the efficacy of haploidentical hematopoietic stem cell transplantation

Novel immunotherapies such as chimeric antigen receptor (CAR) T-cell therapy have strong targets in hematologic malignancies, and the short-term remission rates they achieve are 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).

Combination with chimeric antigen receptor T-cell therapy

For relapsed/refractory ALL, pre-HSCT CAR T-cell therapy could help to decrease the burden of the tumor and reduce the risk of post-transplant relapse. Hu *et al*.[85] reported that the 2-year probabilities of event-free survival, overall survival, and relapse were 76.0%, 84.3%, and 19.7%, respectively, in patients with relapsed/refractory B-ALL who underwent bridging CAR T-cell therapy before HID HSCT. Zhao *et al*.[86] reported that HID HSCT decreased the relapse rate (17.3% *vs*. 67.2%) and increased the leukemia-free survival rate (76.1% *vs*. 32.8%) in patients with relapsed/refractory B-ALL who achieved MRD negativity after CAR T-cell therapy.

Some studies have demonstrated the efficacy of donor-derived CAR T-cell therapy for relapse prophylaxis after allogeneic HSCT. Cheng *et al*.[87] reported that six patients with B-ALL (4 undergoing HID HSCT) with positive MRD received pre-emptive CAR T-cell therapy after allogeneic HSCT; five achieved MRD negativity, and three achieved long-term leukemia-free survival. Zhao *et al*.[88] reported that 12 patients with B-ALL (66.7% undergoing HID HSCT) who had positive MRD after their allogeneic transplant received pre-emptive CAR T-cell therapy and all achieved MRD negativity. Compared to patients who received pre-emptive DLI during the same period, patients receiving pre-emptive CAR T-cell therapy had a significantly lower relapse rate and superior leukemia-free survival.

In addition, Chen *et al*.[89] reported that six patients who experienced relapse after allogeneic HSCT, received donor-derived CAR T-cell therapy, and five achieved MRD-negative complete remission (83.3%); however, four patients experienced relapse again 2-7 months after the CAR T-cell therapy. In a subsequent study with a larger sample,[90] 34 B-ALL patients (22 undergoing HID HSCT) who experienced relapse after allogeneic HSCT received donor-derived CAR T-cell therapy, and 30 achieved MRD-negative complete remission; however, the 18-month overall survival rate was only 30% for those who achieved complete remission. During a median follow-up of 12.7 months, 17 patients experienced a relapse. Thus, the long-term survival of patients treated with CAR T cells remains unsatisfactory among those with post-transplant relapse.

Combination with bispecific T-cell engager antibodies

Blinatumomab was used in patients with relapsed/refractory B-ALL before and after HID HSCT. Wu *et al*.[91] reported that four patients with HLA loss who relapsed after HID HSCT were given blinatumomab: all achieved complete remission, and three achieved MRD negativity. However, when giving patients inotuzumab ozogamicin before or after HID HSCT, attention should be paid to its specific side effects, particularly sinus obstructive syndrome, which occurs with a pooled estimated incidence of 29%.[92]

Combination with new immunotherapies improves the safety of haploidentical hematopoietic stem cell transplantation

Combination with virus-specific cytotoxic T cells

Cytomegalovirus (CMV) infections, particularly refractory/relapsed infections, can significantly increase the risk of non-relapse mortality after HID HSCT. Zhao *et al*.[93] reported that treatment with CMV-specific cytotoxic T cells promotes the restoration of graft-derived endogenous CMV-specific

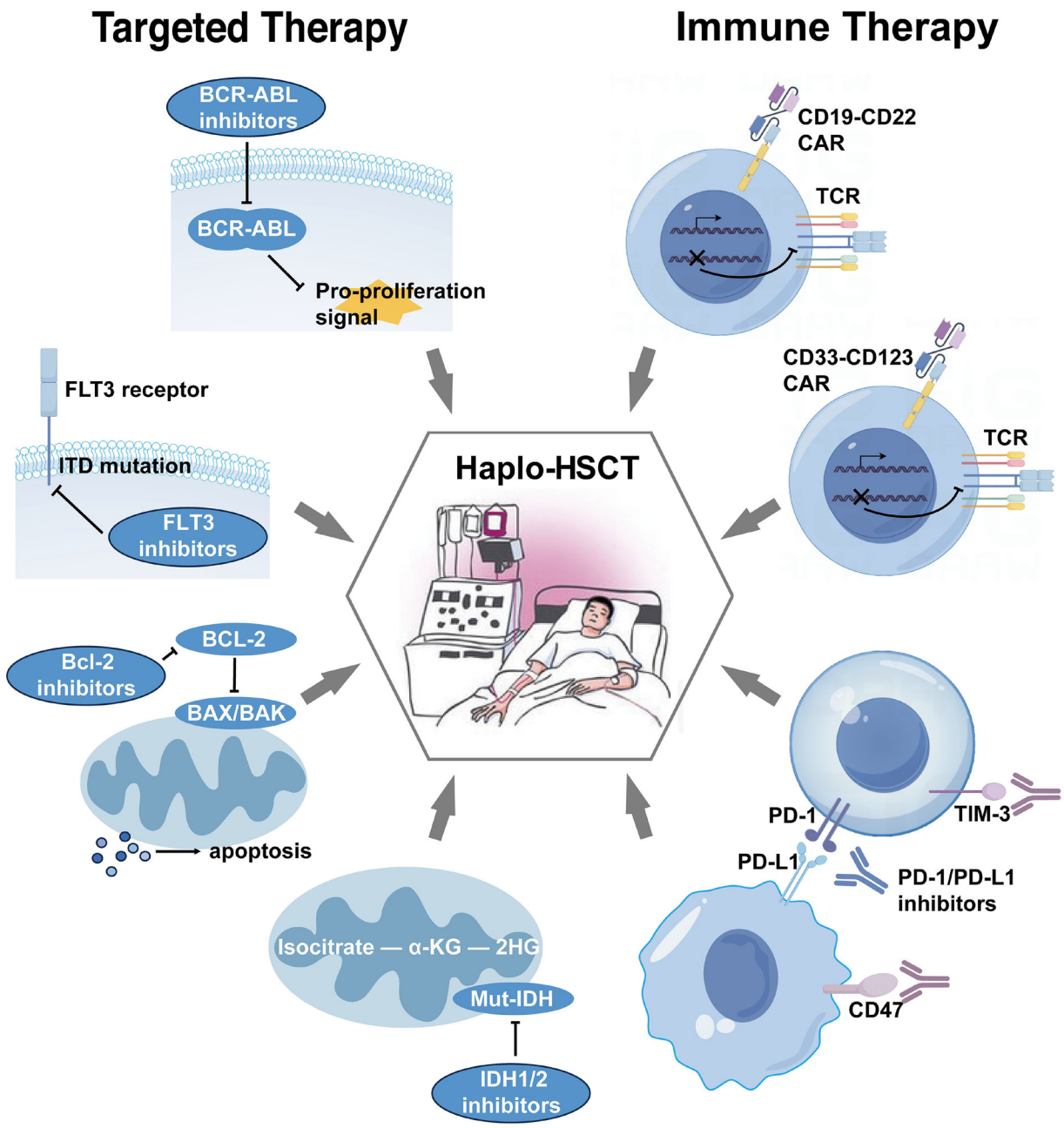

Figure 1. Targeted and immune therapies enhance haploidentical hematopoietic stem cell transplantation. Haploidentical donor (HID) hematopoietic stem cell transplantation (HSCT) could clear tumor cells through different mechanisms, such as the direct killing effects of the conditioning regimen and the graft-*versus*-tumor effect, and it is still the important curative method for most 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 cells, 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. BCR-ABL: breakpoint cluster region-Abelson; FLT3: Fms-like tyrosine kinase 3; ITD: internal tandem duplication; BCL-2: B-cell lymphoma 2 inhibitors; α-KG: alpha-ketoglutarate; 2HG: 2-hydroxyglutarate; IDH1/IDH2, isocitrate dehydrogenase 1/2; CAR: chimeric antigen receptor; TCR: T-cell receptor; PD-1: programmed death-1/programmed death-ligand 1; TIM3: T-cell immunoglobulin and mucin-domain containing-3.

immunity and effectively reduces systemic CMV infections *in vivo*. In addition, first-line therapy with CMV-specific cytotoxic T cells promotes the quantitative and functional recovery of cytotoxic T cells in patients, which is associated with CMV clearance. Recently, Pei *et al.*[94] reported the safety and efficacy of adoptive therapy with CMV-specific cytotoxic T cells for CMV infections in HID HSCT recipients. The cumulative complete response rates in the first, fourth, and sixth weeks after the first CMV-cytotoxic T-cell infusion were 37.9%, 76.8%, and 89.5%, respectively. Among patients who showed a complete response after cytotoxic T-cell infusion, 62.7% did not experience CMV relapse during the follow-up period.

Combination with mesenchymal stem cells

To further decrease the risk of chronic GvHD, Gao *et al.*[95] developed a protocol using mesenchymal stem cells for GvHD prophylaxis after HID HSCT in a multicenter, double-blind randomized controlled trial (ChiCTR-IOR-15006330). Patients were randomly chosen to receive umbilical cord-derived mesenchymal stem cells (3×10^7 cells/100 mL/month) or normal saline (100 mL/month) for >4 months after transplantation. The 2-year cumulative incidence of chronic GvHD in the group given mesenchymal stem cells was 27.4%, which was significantly lower than that in the group not given mesenchymal stem cells (49.0%, P=0.021). Recently, Huang *et al.*[96] evaluated repeated infusions of umbilical cord mesenchymal stem cells

during the early stage (starting 45 days after transplantation) after HID HSCT in an open-label multicenter randomized controlled trial (ChiCTR-IIR-16007806). The group treated with mesenchymal stem cells showed a lower incidence of severe chronic GvHD, grade II-IV acute GvHD, and a better GRFS rate than the control group.

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 non-malignant hematologic disorders, and HID have become the most important alternative donors. The rapid development of novel immunotherapies could help to 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 this procedure, and clarifying the mechanism of immune tolerance after HID HSCT could help to 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 cytotoxic T cells, could help to prevent severe viral infection after HID HSCT. Lastly, new targeted drugs and cellular therapies could help patients with refractory/relapsed hematologic malignancies to achieve disease remission. With the potential for long-term disease control with HID HSCT, patients undergoing this procedure could achieve persistent disease-free survival.

Disclosures

No conflicts of interest to disclose.

Contributions

XH designed the review. XM and XP wrote the manuscript.

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