Current status and prospects of hematopoietic stem cell transplantation in China

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Abstract

Hematopoietic stem cell transplantation (HSCT) is a highly effective and unique medical procedure for the treatment of most hematological malignancies. The first allogeneic transplantation was performed by E. Donnall Thomas in 1957. Since then, the field has evolved and expanded worldwide. The first successful allogenic HSCT (allo-HSCT) in China was conducted in 1981. Although the development of allo-HSCT in China lagged, China has since made considerable contributions to the process of HSCT worldwide, with more than 10,000 HSCTs performed annually. In particular, haploid HSCT (haplo-HSCT) technology represented in the Beijing Protocol has demonstrated similar efficacy to human leukocyte antigen-matched HSCT and has gradually become the pre-dominant choice for allo-HSCT in China. Currently, the number of haplo-HSCT procedures exceeds 5000 per year, and the Beijing Protocol has been greatly improved by implementing updated individualized strategies for controlling complications, relapse, and infection management. In addition, innovative haplo-HSCT technologies developed by different medical transplantation centers, such as Soochow, Zhejiang, Fujian, Chongqing, and Anhui, have emerged, providing inspiration for the refinement of global practice. This review will focus on the current activity in this field and highlight important trends that are vital in China's allo-HSCT process, examining the current viewpoint and future directions.

Keywords: Hematopoietic stem cell transplantation; Haploidentical; China

Introduction

At present, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment for a broad spectrum of hematological malignancies, including acute and chronic leukemia, myelodysplastic syndromes (MDS), lymphomas, and immune or metabolic disorders.[1,2] It has been more than 30 years since the first successful allo-HSCT was performed. Since then, many great achievements have been made in this field. The Chinese Blood and Marrow Transplantation Registry Group (CBMTRG) reported 18,110 HSCTs in a single year (2021), contributing to a total of 90,436 HSCTs since 2008. To date, 174 medical centers have been registered as having a certificate to perform HSCT. Among them, 12,744 allo-HSCTs were performed, accounting for 70.4%, whereas there were 5354 auto-HSCTs, accounting for 29.6%. In particular, there were 7977 (62.6%) haploidentical (haplo) transplants. The five disease entities most suitable for HSCT are acute myeloid leukemia (AML; 4963, 27%), acute lymphoblastic leukemia (ALL; 2903, 16%), multiple myeloma (2544, 14.05%), non-Hodgkin lymphoma (NHL; 2408, 13.30%), and aplastic anemia (AA; 1566, 8.65%).

According to a global survey of the Worldwide Network for Blood and Marrow Transplantation, and taking into considering population size, China has achieved a remarkable transplantation rate (HSCT/10 million population) of 86 in comparison to 53.6 in the whole South East Asia/Western Pacific region and a team density (teams/10 million population) of 1.03.[3,4] Even during the spread of coronavirus disease 2019 (COVID-19) worldwide, the number of transplants in China still increased by 4695 in 2021, indicating that COVID-19 epidemic prevention and control is critical for improving transplantation develop-

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ment.[5] According to the Asia-Pacific Blood and Marrow Transplantation Group report, China (5904) had the highest number of transplants in Asia and the highest increase in total transplants (45.8%). Furthermore, 66.0% of total haploidentical transplants were performed in China.[6] According to the European Society for Blood and Marrow Transplantation (EBMT) activity survey, 18,796 (41%) allo-HSCT and 26,568 (59%) autologous stem cell transplantations were reported; this represented a drop caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic that started early in 2020 in Europe and reflected the varying effect of the pandemic across selected countries and larger cities.[7] According to the Center for International Blood and Marrow Transplant Research (CIBMTR) annual report, the number of allo-HSCTs performed in 2020 in the USA was 8326 and that of autologous was 11,557. Due to the influence of SARS-CoV-2 pandemic, the number of transplants decreased, and COVID-19 may have been reported as a contributory cause of death. In addition, the number of haplo-HSCT procedures has increased rapidly worldwide in recent years. CIBMTR also showed an increase in haploidentical transplants, representing 24% and nearing the ratio of human leukocyte antigen (HLA)-identical sibling transplants (22%).[8] The EBMT reported 3790 haploidentical (haplo) transplants, with a proportion of 20.16%.[7] The rapid growth of allo-HSCT is a result of the increased availability of alternative donors, especially haploidentical donors, entering the new era of "everyone has a donor". Non-first-degree-related donors have been proven as a feasible alternative when first-degree donors are not available for haplo-HSCT.[9] Currently, up to 94% of haplo-HSCTs in China follow the "Beijing Protocol", and the administration of post-transplant cyclophosphamide (PT-Cy) with or without application of the Beijing Protocol has been reported in recent years.

Haploidentical donors have been the largest stem cell source in China since 2013. The continuous updates of this approach should be progressively integrated worldwide, which would benefit large populations of patients.

Where Do We Stand?

The number of HLA-matched donors has been insufficient to meet the increasing need for allo-HSCT in China, and the current status of HSCT based on different diseases was summarized as [Table 1]. Each immediate family member could be a haploidentical donor, increasing the number of available donors. To overcome the HLA barrier and induce immune tolerance in haplo-HSCT, several developments have been made, such as T cell depletion (TCD),[10] unmanipulated grafts with granulocyte colony-stimulating factor (G-CSF) plus anti-thymocyte globulin (ATG)-based regimens,[11] and PT-Cy-based regimens.[12,13] In 2000, according to the theory of G-CSF inducing immune tolerance, the Peking University Institute of Hematology team established a protocol for unmanipulated haplo-HSCT using a myeloablative conditioning regimen with G-CSF-mobilized/primed grafts, named the Beijing Protocol,[14] which is characterized by individualized and optimized conditioning and modified grafts. Since then, the protocol has been perfected in terms of optimizing technological systems, forming a unique Chinese haplo-HSCT protocol.[15] In addition, because of the shift from TCD grafts to unmanipulated bone marrow (BM) and/or peripheral blood (PB) harvests, haplo-HSCT is much easier to perform than before.[16] The outcomes of haplo-HSCT following the Beijing Protocol have shown to be comparable to those of HLA-matched sibling HSCT in multicenter, prospective, or registry-based studies.[17] The development of haplo-HSCT has shown advantages in different hematological diseases. For adults with acute leukemia, haplo-HSCT showed outcomes in terms of 3-year disease-free survival (DFS) (74% *vs.* 78%, $P = 0.34$) and overall survival (OS) (79% *vs.* 82%, $P = 0.36$) that were similar to matched sibling donor transplantation (MSDT) in complete remission 1 (CR1).[18] The survival benefit should also be observed in children.[19,20] Yu *et al*[21] reported comparable outcomes in 111 cases of refractory AML following MSDT or haplo-HSCT in terms of the 5-year cumulative incidence of relapse (CIR) (32% *vs.* 23%, $P = 0.243$) and OS (44% *vs.* 50%, $P = 0.947$). The First Affiliated Hospital of Zhejiang University School of Medicine team developed an approach of T cell-replete haplo-HSCT with low-dose ATG, which improved the outcomes of high-risk leukemia patients.[22] In a recent prospective multicenter study of young adults with standard-risk ALL in CR1 in the absence of HLA-matched donors, haplo-HSCT showed a lower 2-year CIR (12.8% *vs.* 46.7%, $P = 0.0017$) and better 2-year DFS (80.9% *vs.*

Table 1: Current status of allo-HSCT according to different diseases in China.

Items	AML	ALL	NHL	AA	MDS	Thalassaemia	CML
HID	3133	1890	217	855	820	415	132
	66.36%	67.05%	62.72%	54.91%	61.65%	53.55%	66.67%
MSD	915	492	77	350	327	177	33
	19.38%	17.45%	22.25%	22.48%	24.59%	22.84%	16.67%
URD	468	314	32	248	128	172	24
	9.91%	11.14%	9.25%	15.93%	9.62%	22.19%	12.12%
CBT	205	123	20	104	55	11	9
	4.34%	4.36%	5.78%	6.68%	4.14%	1.42%	4.55%
Total	4721	2819	346	1557	1330	775	198

AA: aplastic anemia; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CBT: cord blood transplantation; CML: chronic myeloid leukemia; HID: haploidentical donor; MDS: myelodysplastic syndromes; MM: multiple myeloma; MSD: matched sibling donor; NHL: non-Hodgkin lymphoma; URD: unrelated donor.

51.1%, $P = 0.0116$) and OS (91.2% *vs.* 75.7, $P = 0.0408$) than chemotherapy.[23] For Philadelphia-negative high-risk ALL patients undergoing haplo-HSCT and MSDT, 3-year DFS (61% *vs.* 60%, $P = 0.91$) and OS (68% *vs.* 66%, $P = 0.81$) were comparable[24] and were the same as the standard-risk ALL.[25] The Nanfang Hospital group illustrated that for myelodysplastic syndrome with excess blasts, upfront transplantation was preferable to pre-transplant cytoreductive therapy.[26] The First Affiliated Hospital of Soochow University group has continuously committed to optimizing the haplo-HSCT system, which showed comparable efficacy to MSDT for patients with refractory/relapsed NHL; the progression-free survival (PFS) rate was 60.5% to 54.3% ($P = 0.938$), and the OS rate was 67.9% to 55.7% ($P = 0.460$).[27] In addition, haplo-HSCT is a beneficial and feasible option for non-malignant hematological diseases.[28-30] Haplo-HSCT demonstrated comparable failure-free survival (FFS; 86.8% *vs.* 80.3%) as a salvage treatment for severe AA (SAA).[31] For SAA, the estimated 4-year FFS ($77.8 \pm 3.7\%$ *vs.* $48.0 \pm 3.6\%$, $P < 0.0001$) was compared between first-line haplo-HSCT and immunosuppressive therapy, with a better health-related quality of life score obtained for haplo-HSCT.[32]

With the efforts of different transplant centers in China, the efficacy, safety and feasibility of the Beijing Protocol in haplo-HSCT have been confirmed for treating hematopoietic diseases; the findings of these studies have been summarized as a consensus, thereby inspiring the refinement of global clinical practice and making great progress.[33]

What Do We Face?

Comparison between allo-HSCT regimens

The development of haplo-HSCT includes three main approaches: G-CSF plus ATG-based regimens with unmanipulated T cell replete grafts that originated in the Beijing Protocol[34]; PT-Cy-based regimens with unmanipulated T cell replete grafts that originated from the Baltimore group[35]; and TCD-based regimens that originated from the Perugia group in Italy.[10] The former two approaches are the most verified regimens. While the Beijing protocol for haplo-HSCT combines myeloablative conditioning, reinfusion of G-CSF-primed BM plus PB relies on ATG for the prevention of GVHD (graft-versus-host disease), and the Baltimore protocol with reduced intensity conditioning and high-dose PT-Cy is predominant. PT-Cy is mostly used in haplo-HSCT in Western countries, and research from Johns Hopkins in Baltimore showed that the non-relapse mortality (NRM) at day 100 and 2 years was 9% and 17%, respectively, and the 2-year OS and event-free survival were 55% and 39%, respectively.[36] However, PT-Cy is also associated with problems such as hematopoiesis suppression, delayed engraftment, and slow immune reconstitution, thus leading to increased infection rates. The application of the Beijing Protocol in therapy needs more attention to prevent GVHD. Furthermore, the poor remission rate or refractory disease before HSCT may be a situation in which the Beijing Protocol is the preferred platform.[37,38] The Beijing Protocol also acted as a very effective choice for young SAA patients because there was no significant difference in 5-year OS or GVHD between haplo-HSCT and MSDT.[39] The results of this meta-analysis also supported the role of haplo-HSCT with the Beijing Protocol, which could achieve comparable clinical outcomes in terms of OS, PFS, NRM, and relapse rate, and is better in terms of decreasing transplantation complications, thus supporting haplo-HSCT as a very valid option in the transplantation field.[40,41] The first formal comparison of PT-Cy-based and ATG/G-CSF regimens for haplo-HSCT in patients with SAA was conducted, showing that the ATG/G-CSF regimen was potentially superior to the PT-Cy-based regimen because it resulted in faster myeloid engraftment and comparable OS, FFS, and GVHD. However, prospective randomized control studies with larger patient cohorts are required to confirm the preliminary results.[42] Similarly, according to a comparison of G-CSF/ATG and PTCy use in haplo-HSCT for hematological malignancies between January 2013 and March 2018 using data reported to the CBMTRG, G-CSF/ATG achieved better engraftment, PFS, and OS, and a lower incidence of NRM than PT-Cy.[43]

Complication challenges include graft failure, GVHD, and relapse

General complication challenges such as poor graft function (PGF), GVHD, and recurrence after transplantation of allo-HSCT could not be avoided in haplo-HSCT. The Chinese transplant team aims to address the above problems to optimize haplo-HSCT, thus achieving an international advanced level.

Graft failure

PGF is defined as two or three cytopenic counts beyond day 28 post-HSCT with donor chimerism,[44] and is associated with a lower survival rate and is known to occur in 5% to 27% of patients.[45] Despite advances in haplo-HSCT protocols, there still remains a need to reduce PGF, and the modified Beijing Protocol has been associated with a 4% to 5% incidence, which still compromises the success of haplo-HSCT.[46] The occurrence of PGF may be correlated with donor-specific anti-HLA antibody (DSA) for the development of primary PGF.[47] The Beijing team adopts rituximab (anti-CD20 monoclonal antibody) to clear DSA, thus decreasing the incidence of PGF. They reported that a single dose of 375 mg/m^2 rituximab was enough to show efficacy in preventing the onset of PGF.[48] In addition, ongoing advances in the understanding of the BM microenvironment in PGF patients may suggest novel strategies to promote hematopoietic regeneration in individuals with PGF following HSCT. Because a reduced amount of BM endothelial progenitor cells (EPCs) is an independent risk factor for PGF occurrence,[49] atorvastatin treatment could quantitatively and functionally improve BM EPCs from PGF through downregulation of the p38 MAPK pathway.[50] Prophylactic oral N-acetyl-l-cysteine could safely and effectively improve hematopoiesis and megakaryocytopoiesis by repairing BM hematopoietic stem cells (HSCs), endothelial cells (ECs), and mesenchymal

stem cells (MSCs) in PGF post-haplo-HSCT.[51] The Beijing team also proposed that all-trans retinoic acid could protect MSCs from dysfunction and apoptosis by upregulating deoxyribonucleic acid (DNA) hypermethylation of the *IL1B* promoter, thus restoring the thrombopoietic niche.[52] Eltrombopag, an oral thrombopoietin receptor agonist, has also been reported to be a safe and effective therapy for improving graft function.[53] For patients with graft failure after the first transplantation, a second haplo-HSCT using a fludarabine/cyclophosphamide regimen from a different donor was a promising salvage option, and the OS and DFS at 1 year were 56.6% and 48.4%, respectively.[54]

Graft-Versus-Host Disease

As mentioned above, the rates of GVHD were comparable between haplo-HSCT and MSDT with the Beijing Protocol. Based on the 9-year follow-up of the largest haplo-HSCT cohort in the Beijing Protocol, the incidence of grade II–IV acute GVHD (aGVHD) was 43%, and the 2-year cumulative incidence of total chronic GVHD (cGVHD) was 53%, which is the most common mortality after HSCT.[55] To better and more precisely predict or judge the severity of GVHD after haplo-GVHD, biomarkers are important. Xinqiao Hospital reported that the combination of Toll-like receptor 4 (TLR4), TNF receptor 1 (TNFR1), transforming growth factor-β (TGF-β), and elafin could be a new four-biomarker panel to assist aGVHD diagnosis,[56] and chemokine (C-X-C motif) ligand 9 (CXCL9) and C-C Motif Chemokine Ligand 17 (CCL17) could be adopted as cGVHD severity and tissue-specific biomarkers.[57] In addition, cluster of differentiation 4/cluster of differentiation 8 (CD4/CD8) ratios in BM allografts ≥1.16, $CD56^{bright}$ natural killer (NK) cells in allografts $>1.9 \times 10^6$/kg, monocytic myeloid-derived suppressor cells (MDSCs) in allografts $<1.22 \times 10^7$/kg, and other components of grafts played predictive roles in the onset of aGVHD.[58-60] To improve long-term outcomes and decrease NRM in haplo-HSCT patients, the joint use of ATG and PT-Cy showed better outcomes.[61] The Beijing team first discovered in a mouse model that ATG combined with low-dose PT-Cy could reduce GVHD incidence by promoting regulatory T cell (Treg) reconstitution.[62] In subsequent research to assess the efficacy of PT-Cy in conjunction with ATG for preventing GVHD, researchers confirmed that the addition of low-dose PT-Cy on the basis of the Beijing Protocol could reduce III- to IV-degree aGVHD (5% *vs.* 18%, $P = 0.003$), cGVHD (30% *vs.* 44%, $P = 0.07$), and NRM (6% *vs.* 15%, $P = 0.045$). The studies resulted in the "Sino-US Protocol," which aimed to improve the prognosis of haplo-HSCT and is a further improvement and optimization of the current protocol. In addition, low-dose glucocorticoid prophylaxis could reduce GVHD and thus reduce the total dose of steroids, which might contribute to a lower incidence of infections and a superior GVHD-free, relapse-free survival (GRFS).[63] In addition to adjusting the regimen, cellular therapy has shown increasing significance in managing GVHD. In a phase II multicenter clinical trial at Xinqiao Hospital, which adopted umbilical cord-derived mesenchymal stromal cells in the prophylaxis of chronic GVHD, the 2-year cumulative incidence of cGVHD was reduced in the MSC group compared with the non-MSC group (27.4% *vs.* 49.0%, $P = 0.021$) without increasing the relapse risk.[64] This study might provide hope for preventing cGVHD after haplo-HSCT. Mechanistic research comparing the efficacy of different tissue-derived MSCs in controlling GVHD found that human umbilical cord-derived mesenchymal stem cells (HUCMSCs) decrease GVHD more effectively by recruiting MDSCs to target tissues through the CXCL1–CXCR2 axis.[65] For cGVHD treatment, in Xinqiao Hospital, sirolimus combined with calcineurin inhibitor had a better effect on steroid-refractor (SR) cGVHD[66] with relatively mild side effects, and was thus suitable for long-term treatment of cGVHD. In addition, in SAA, co-transplantation with MSCs for haplo-HSCT is encouraging and is associated with high rates of engraftment and survival.[67] Moreover, the Zhejiang team found that ruxolitinib combined with etanercept can reduce severe III–IV SR-aGVHD, and a marked reduction of ≥75% in daily corticosteroid dosing was observed in 75.4% of patients at day 28.[68] They subsequently performed a 41-patient single-site case series in which ruxolitinib demonstrated a significant response in patients with SR-cGVHD and a reasonably well-tolerated safety profile, suggesting ruxolitinib as a promising treatment option in SR-cGVHD.[69] Additionally, 7.5 mg/kg ATG as GVHD prophylaxis in haplo-HSCT was associated with reduced viral infections without increased GVHD.[70] The Fujian team proposed a promising approach in which sequential transplantation of haplo-cord could improve the survival outcomes of patients with relapsed/refractory hematological malignancies with lower GVHD.[71] The Xinqiao Hospital team has built a composite technology system based on "Remodeling the hematopoietic microenvironment" for refractory leukemia to formulate the therapy roadmap and comprehensively improve HSCT efficacy by decreasing GVHD and improving GVL. The 2-year OS increased by 21.5%.[72-74]

Relapse

For patients undergoing haplo-HSCT based on the Beijing Protocol, the 2-year cumulative incidences of relapse were 15% and 26% in the standard-risk and high-risk groups, respectively,[55] but the incidence of relapse-related mortality was reported to be no different between haplo-HSCT and MSDT (15.6% *vs.* 16.7%, $P = 0.943$).[75] Donor lymphocyte infusion (DLI) is an effective method of preventing relapse in patients. The Beijing team adopted PB mobilized by G-CSF combined with low-dose immunosuppressive agents to establish a modified DLI (mDLI) recurrence prevention system. A series of clinical studies conducted by the Beijing team showed that mDLI can be used effectively to prevent and treat relapse in haplo-HSCT patients, thus improving the efficacy of transplantation,[76] and efficacy was confirmed by the Johns Hopkins University team and the Zhejiang team. In addition, for the Beijing Protocol, the strategies for relapse are mineral residential disease (MRD)-based, multiple chemotherapy combined with DLI guided by MRD, and GVHD-guided multiple DLIs, which could reduce the relapse rate compared with single chemotherapy combined with DLI (22% *vs.* 56%, $P < 0.001$), and

the OS rate was significantly increased (78% *vs.* 44%, $P < 0.001$) in patients with refractory/relapsed ALL after transplantation.[77] In addition, targeted drugs such as tyrosine kinase inhibitors have been successfully used for relapse treatment.[78] Fms-like tyrosine kinase 3 (FLT3) internal tandem duplication (FLT3-ITD) mutations occur in approximately 25% of adult AMLs. Even though allo-HSCT could improve survival, the relapse rate among those with FLT3-ITD mutations remains relatively high. Battipaglia *et al*[79] reported that sorafenib was adopted to treat patients after HSCT, and the 1-year OS and leukemia free survival (LFS) were 92% ± 6% and 92% ± 5%, respectively. Nanfang Hospital launched an open-label, randomized phase 3 trial at seven hospitals in China to investigate the efficacy and tolerability of sorafenib maintenance post-transplantation in patients with FLT3-ITD-mutated ALL, with a 1-year CIR that was reduced to 7.0% compared with 24.5% in the control group ($P = 0.001$).[80]

Prospects for the future

Further developments and improvements in the haplo-HSCT system have been simultaneously implemented from several aspects. First, how to select donors to strengthen graft versus leukemia effects remains unclear. Second, mechanistic research on immune tolerance for the separate effects of GVHD and GVL. Last but not least, combination therapies with novel drugs are in the pipeline.

Donor preparation and risk stratification

Although HSCT represents the only curative therapy for hematological malignancies, donor T cells failing to reach the tolerant state in the host microenvironment leads to severe GVHD and threatens the survival of patients. By characterizing the gene expression profile in tolerant T cells, the dynamics of transcriptomes in a physiological T cell tolerance model can be determined. Moreover, the Beijing team conducted the first prospective RCT across 23 transplantation centers to demonstrate that ATG could effectively decrease the incidence rate of grade 2 to 4 aGVHD (13.7% *vs.* 27.0%, $P = 0.007$), 2-year overall cGVHD (27.9% *vs.* 52.5%, $P < 0.001$), and 2-year extensive cGVHD (8.5% *vs.* 23.2%, $P = 0.029$) after HSCT compared with cyclosporine treatment without affecting the CIR or NRM.[81]

Balance of GVHD and GVL

Considering the control of GVHD, the establishment of a GVHD prevention prediction system and the study of the underlying mechanism were used to establish a concrete foundation for the transfer from precision medicine to clinical practice. Patients could be stratified into high- and low-risk sub-groups according to CD4/CD8 ratios. The cumulative incidence of grade II to IV acute GVHD was reduced from 48.1% to 20.9% by prophylaxis in the high-risk group treated with low-dose glucocorticoids.[82] In addition, the Beijing team adopts G-CSF mobilized PB stem cell collection infusion combined with DLI, followed by short-term immunosuppressive agents, to prevent and treat recurrence after haplo-HSCT, which is safe and effective. According to risk-stratified treatment, a complete mDLI system has been formed, which includes therapeutic mDLI for relapsed patients, interventional DLI for MRD-positive patients, and preventive mDLI for patients in a relapse/refractory state before transplantation. Chemotherapy combined with DLI therapy was guided by dual indicators of MRD and GVHD after DLI. Compared with chemotherapy combined with DLI alone, the relapse rate was significantly reduced (22% *vs.* 56%, $P < 0.001$), and the LFS and OS rates increased significantly (71% *vs.* 35%, $P < 0.001$; 78% *vs.* 44%, $P < 0.001$).[83]

Combination of novel treatments and HSCTs

Novel treatments include chimeric antigen receptor-T (CAR-T) cells and histone deacetylation inhibitors, demethylation agents, monoclonal antibodies, immunomodulatory drugs, and tumor vaccines. CAR-T cell therapy has shown promising efficacy in salvaging relapsed/refractory B-ALL patients after HSCT and is widely recognized worldwide, having brought hope for patients with hematological malignancies.[84,85] Therefore, a new treatment model combining cutting-edge therapy and HSCT is emerging. The combination of CAR-T and HSCT has become an effective means to improve efficacy before, during, and after HSCT. Before HSCT, CAR-T cell therapy could help clear residual tumor tissue or be used to reduce the tumor burden before the regimen. During HSCT, CAR-T cell therapy could help better bridge HSCT and reduce relapse. An open-label pragmatic clinical trial from Wuhan suggested that CAR-T should be bridged to transplantation, resulting in better LFS.[86] For patients who experience relapse or progression after HSCT, CAR-T cell therapy could serve as a rescue treatment. In addition, CAR-T cell therapy could be adopted as a consolidation or maintenance treatment to reduce the relapse risk in high-risk patients. However, in CAR-T cell therapy for refractory/relapsed hematopoietic malignancies, although the remission rate was encouraging, the high long-term relapse rate needs to be solved.[87] CD19-targeted CAR-T cell therapy against R/R ALL achieved a CR rate of 92.3%. However, relapse after CAR-T cell therapy remains a pre-dominant obstacle, with a 20% to 70% relapse rate when the follow-up period was sufficiently long. Xinqiao Hospital reported that the therapy of B-ALL subjects experiencing relapse after transplantation with donor-derived CAR-T cells was safe and effective; the CR rate was up to 79.05%, and outcomes seem comparable to those achieved with alternative therapies, but data from a randomized trial are lacking.[88] Allogeneic CAR-T cells can effectively treat malignancies that progress after HSCT. The Tongji group also reported that haplo-CAR-T cell therapy could effectively control lymphoma that failed to respond to autologous CAR-T cell therapy and thus may be one possible regimen before "universal" CAR-T cell therapy. In addition, antigen-specific T cell therapies will play a role in HSCT.[89] Maintenance therapy after HSCT is the most effective therapy to reduce relapse. Alternative drugs include FLT3 inhibitors, histone deacetylation inhibitors, demethylation agents, monoclonal antibodies, immunomodulatory drugs, and tumor vaccines. The demethylating agent azacitidine could increase Tregs and induce CD8+ T cell reactions, which may be one of the mechanisms of graft versus leukemia effect enhancement

without increasing GVHD.[90] In addition, the combination of hypomethylating agents could synergistically promote the elimination of AML and prevent relapse after HSCT. The Xinqiao group launched a study to investigate recombinant human G-CSF combined with decitabine (Dec) for relapse prophylaxis in high-risk AML (HR-AML) patients after HSCT. The results indicated that the estimated 2-year CIR in the G-Dec group was lower (15.0% *vs.* 38.3%, $P < 0.01$) and that there was no significant difference in the 2-year cumulative incidence of cGVHD (23.0% *vs.* 21.7%, $P < 0.01$ and $P = 0.82$, respectively).[73] The First Affiliated Hospital of Soochow University group also conducted maintenance therapy with Dec after HSCT to prevent relapse of HR-AML with a significant reduction in the 3-year CIR in the Dec and control groups (5.9% *vs.* 45.3%, $P = 0.002$).[91] Moreover, their data indicated that 5-day low-dose Dec, as part of a modified Bu–Cy conditioning regimen, may confer a survival advantage in HR-AML (2-year OS 78.3% *vs.* 62.9%).[92] Recently, the FLT3 inhibitor midostaurin as a maintenance treatment for FLT3-positive patients after HSCT significantly improved the survival of CR1 patients.[93]

Conclusion

The establishment and improvement of haplo-HSCT technology systems has signified the coming of the new era of "everyone has a donor". With its continuous improvement and optimization, the allo-HSCT system is becoming more complete, and more researchers are participating in academic exchanges. In the past 5 years, transplantation-related Science Citation Index (SCI) publications from China account for 13% of the total publications worldwide, among which, depending on the different types of blood disorders, the SCI publication ratio in AML, ALL, AA, and MDS is 25.8%, 38.5%, 31.1%, and 20.2%, respectively. In addition, the proportion of Chinese guidelines/consensus to international guidelines/consensus is increasing to 59.6% and 43.8% about transplantation norms and complication management, respectively. As for other stem cell sources in allo-HSCT, umbilical cord blood transplantation in China also provides more choice for patients.[94,95] Moreover, based on the mechanism of HSCT, microtransplantation may bring hope for older patients with AML who are unfit for HSCT.[96,97]

The transplantation systems of different medical centers have their own characteristics, and all have made contributions to improving the transplantation technology, aiming to make HSCT much simpler and controllable with regard to manufacturing and more stable in terms of efficacy. However, the demands of patients have not been satisfied in the current situation due to the population baseline. Beyond the endeavors made to improve the depth of HSCT, the speed of HSCT technology dissemination also requires attention. Furthermore, scholars in China have already designed clinical trials to combine novel therapies such as CAR-T cell therapy and molecular drugs with haplo-HSCT, but the combination that brings the most benefit remains to be explored. Furthermore, survival is no longer the only goal, and promoting physical and psychological health recovery among patients to help them return to society and family life should receive more attention. These points are of great importance in the future [Figure 1].

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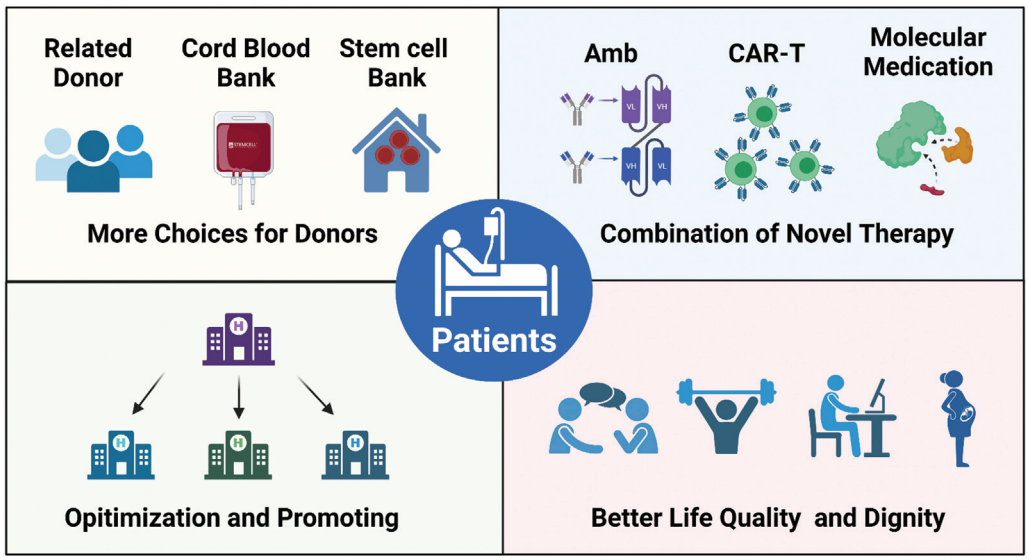

Figure 1: The future of allo-HSCT. allo-HSCT: Allogenic Hematopoietic stem cell transplantation; CAR-T: Chimeric antigen receptor-T.

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Conflicts of interest

None.

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