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News & Views

A vision for the future of allogeneic hematopoietic stem cell transplantation in the next decade

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The whole field of hematological malignancies has experienced a huge breakthrough during the past 40 years. Major methodological progress in cytogenetics (e.g., fluorescence *in situ* hybridization, FISH), immunophenotyping (e.g., multicolor flow cytometers), and molecular biology (with the discovery of numerous tumor molecular markers by polymerase chain reaction and, more recently, next-generation sequencing) has paved the way for the new concept of detecting and monitoring undetectable minimal residual disease (uMRD) and the engineering of multiple new targeted therapies, such as tyrosine kinase inhibitors and various immunotherapies, including monoclonal antibodies combined or not with antitumor agents, bispecific T-cell-engaging (BiTE) antibodies and chimeric antigen receptor T (CAR-T) cells (Supplementary Text 1 online).

Additionally, allogeneic hematopoietic stem cell transplantation (allo-HSCT) has also been improved in several aspects: stem cells are now mostly collected by cytapheresis, and nonrelapse mortality (NRM) rates have decreased to less than 20% in experienced centers due to the development of reduced intensity conditioning (RIC), refined graft-versus-host disease (GVHD) prophylaxis, and improved infection control practices. Meanwhile, most of all, it has recently become possible to find a donor for practically every patient in need, thanks to an international database of unrelated voluntary donors (approximately 40 million) and the feasibility of transplants from haploidentical intrafamily donors (HIDs) (Supplementary Text 2 online).

Allo-HSCT has been widely used to treat malignant hematological neoplasms and nonmalignant hematological disorders. Nearly 650,000 allogeneic transplants have been performed thus far worldwide [1]. Additionally, novel targeted therapies have resulted in great improvement for some—if not all—hematological malignancies. We consider that these new agents will probably not replace allo-HSCT to become the "ultimate curative choice" for all hematological malignancies in the near future but that they might combine with and strengthen allo-HSCT as perfect partners. In this article, we summarize these cutting-edge aspects and address the debates that may determine the new trends for allo-HSCT in the next decade.

How to choose the ideal donor? Human leukocyte antigen (HLA) is an important part of the immune system that encodes cell surface molecules specialized to present antigenic peptides to T-cell receptors. Previously, the availability of HLA-matched donors was essential for successful allo-HSCT, and there has long been a shortage of donors. Recently, novel HID-HSCT regimens such as the "Beijing Protocol", the "Baltimore Protocol" and other technologies such as "TCR αβ/CD19$^+$ depletion" have been developed to overcome these barriers, thereby dramatically improving overall survival from 10%–30% to 60%–70% [2–4]. There is growing evidence that the level of HLA disparity (numbers of mismatched HLA) is not associated with prognosis, whereas HID-HSCT generally demonstrated similar NRM, disease-free survival (DFS) and overall survival (OS) rates compared to allo-HSCT with MSD or matched unrelated donors in most allo-HSCT indications. In recent decades, the consensus in Europe has been to consider HLA MSDs as the preferred first donor choice for allo-HSCT; in contrast, HID-HSCT has been a mostly "*de facto*" first choice in China, where the availability of MSDs is limited. Moreover, preliminary results of a registry-based study of the European Society of Blood and Marrow Transplantation (EBMT) also support the possibility of transplantation with HLA-mismatched donors beyond HIDs (Supplementary Text 3 online). Therefore, a series of new questions emerge that were not even conceivable in the past decade, e.g., will HLA disparity still matter for allo-HSCT in the near future? and will MSDs remain the first choice as an ideal donor?

At present, there is some indication that HIDs might reduce the relapse rate over MSDs for patients with high-risk hematologic malignancy. In a mouse model, superior graft-versus-leukemia (GVL) activity, such as decreased apoptosis and increased cytotoxic cytokine secretion by T or natural killer cells, has been shown in HID-HSCT compared with syngeneic transplantation [5]. For high-risk AML patients, EBMT reported that for male recipients, the outcome was superior with HID transplant than with an MSD sister [6]. HID-HSCT was also found to be superior to MSD-HSCT in eliminating post-HSCT MRD and improving DFS/OS in pre-HSCT

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MRD$^+$ patients with acute myelogenous leukemia (AML) or acute lymphoblastic leukemia (ALL) or reducing the relapse rate in relapsed Hodgkin lymphoma. Therefore, the Chinese consensus recommended that HIDs are preferable to MSDs transplantation for high-risk leukemia in experienced centers [7]. It remains unclear whether such a stronger GVL is observed in different HID-HSCT models throughout the world. Additionally, other factors, such as the permissive mismatch of specific HLA loci, killer cell immunoglobulin-like receptor (KIR) genotyping, and donor age and sex, are important in donor selection. It may be feasible to use an approach where donors would no longer be selected necessarily only according to the HLA system compatibility as in the past 50 years or so (Supplementary Text 4 online).

As GVHD remains a considerable obstacle in both HLA-matched and HLA-mismatched HSCT, there are other decisive factors in addition to HLA disparity that need further improvement. The mechanism to bypass the HLA barrier warrants, however, more in-depth investigations that examine the metabolism of immune cells, elucidate the crosstalk between mucosal microbiota and immune systems, and manipulate immune reconstitution to favor GVHD/GVL separation. Such a major step would have a major impact on donor selection and HSCT (Supplementary Text 5 online).

Combination with immune therapies and targeted molecular agents might strengthen allo-HSCT. Allo-HSCT has been the most important and curative method to treat acute leukemia. Indeed, it is presently the preferred approach for patients with AML or myelodysplastic syndromes (MDS) classified into intermediate or poor risk categories. The situation is more complex for lymphoid malignancies and first of all ALL in adult patients. There has been an important gap in survival between patients transplanted in complete remission (CR) and those transplanted while refractory or in relapse (R/R status); for example, the 5-year OS of R/R ALL has been only half of the OS of patients transplanted in CR [8]. Newly developed targeted therapies, including molecular agents and immune therapy, bring considerable hope to these R/R patients (Supplementary Text 6 online).

CAR-T cells are T cells that have been genetically engineered to produce an artificial T-cell receptor for use in immunotherapy. From the first application of CAR-T for the treatment of ALL in 2013 to the United States Food and Drug Administration's (FDA) first approval of Kymriah (tisagenlecleucel) for patients with advanced lymphoblastic malignancies in 2017, clinical studies of CAR-T therapy have experienced blooming growth worldwide. For example, the most widely applied CAR-T treatment, which targets CD19, has resulted in remission rates of 83%–93% for adults and 67%–90% for pediatric patients. More recently, CAR-T targeting CD7 for R/R T-cell ALL has also resulted in encouraging CR rates of 85%–93% [9]. BiTE antibodies or mono-antibodies are also important immune therapies for R/R B-ALL (Supplementary Text 7 online).

Nevertheless, when we question whether "targeted therapy or immune therapy might take precedence over allo-HSCT", we should note that, in contrast with children, the duration of response remains low with no plateau, and the long-term survival is only 20%–40% in adults with ALL. Therefore, considering the perfect short-term response along with the high risk of disease recurrence, CAR-T cells may be used as a bridge to allo-HSCT or incorporated into conditioning regimens rather than as a replacement [7]. For example, allo-HSCT for ALL not in CR1 in Europe has increased by 40% in the past decade due to the development of immune therapy [10]. In addition, novel immune therapies targeting hematological malignancies beyond CAR T cells, such as CAR natural killer cells and engineered TCR T cells, have been developed and might further improve the outcomes (Supplementary Text 8 online).

Novel molecular agents also improve remission by targeting specific pathways of hematological malignancies, such as BCR-ABL (for chronic myelocytic leukemia), FMS like tyrosine kinase 3 (FLT-3), B-cell lymphoma 2 (BCL-2), and isocitrate dehydrogenase 1 (IDH1) for AML. The FLT3 inhibitor gilteritinib has resulted in a superior CR rate when compared to chemotherapy for patients with R/R AML. Of even more considerable interest, the combination of a BCL-2 inhibitor (venetoclax) and DNA hypomethylating agents (azacitidine) has shown a synergistic effect in R/R AML suggesting that these new therapeutic platforms may also extend the recruitment of candidates for allo-HSCT (Supplementary Text 9 online).

Relapse remains the major cause of death post-HSCT and accounts for 56%–60% of the overall mortality. Targeted therapies not only will be used to bridge to transplant but also have a role in preventing relapse post HSCT. Maintenance with sorafenib for FLT3$^+$ AML resulted in a lower relapse rate and improved DFS compared with the control group in two phase III randomized trials (Supplementary Text 10 online). For ALL-B patients with recurrence of MRD post-HSCT, preemptive CAR-T therapy has a greater chance of achieving MRD negativity (100% vs. 66.7%, $P = 0.032$) and more rapidly (14 d vs. 43 d, $P < 0.001$) than donor lymphocyte infusion [11]. One can also consider CAR-T therapy administered preemptively as a new modern targeted DLI approach.

In addition to controlling the original diseases, immune therapies of a different nature have also contributed to improving the management of allo-HSCT complications, such as mesenchymal stromal cells (MSCs) for treating steroid-resistant GVHD and specific cytotoxic T lymphocyte (CTL) or T-cell receptor (TCR) therapy to prevent viral infections by restoring endogenous virus-specific immunity (Supplementary Text 11 online).

These results indicate the possibility of combining allo-HSCT with immune therapies and targeted molecular agents pre- and post-transplant in the near future.

There will be sustained growth of allo-HSCT in the next decade. Donor availability, refined allo-HSCT with lower NRM rates, and increased candidates played a key role in supporting the sustained growth of allo-HSCT.

In China, the prevalence of HIDs increased twenty-fold to 6000 cases per year, and they have become the largest source of allo-HSCT activity since 2013, accounting for more than 60% of all allo-HSCT activity in 2019 [12]. For Europe and the USA, HID-HSCT activity has also increased tenfold in the last decade, from less than 5% to approximately 20% of allo-HSCT cases [10,13]. The development of HID-HSCT has led to a new era in which "every-one has a donor" and facilitates sustained growth potential for allo-HSCT in the next decade.

Several key factors contributed to reducing NRM rates of allo-HSCT, including but not limited to: (1) GVHD prophylaxis and treatment have been refined. For example, the optimization of antithymocyte globulin (ATG) dosage in the "Beijing Protocol" has resulted in comparable GVHD incidence but a decreased virus-related death rate [14]; combination of the "Beijing Protocol" and "Baltimore Protocol" further reduces GVHD related death in GVHD high-risk patients. Additionally, refined GVHD treatments by ruxolitinib, basiliximab have become available. (2) RIC conditioning regimens improve the safety of allo-HSCT, especially in elderly patients, so that age alone is no longer a barrier to successful HSCT; novel second HSCT protocols with a RIC regimen have rescued patients from poor engraftment or rejection post-allo-HSCT, but caution must be taken in many situations if the NRM rate decreases at the cost of increased relapse rates. (3) Improved infection control practices have been developed, including novel antiviral agents, such as letermovir and maribavir for cytomegalovirus, as well as immune therapy. All these developments have reduced the NRM of HID-HSCT from 50% to 10%–20% in experienced centers and might facilitate the allo-HSCT procedure more

broadly in the near future. Nevertheless, currently, it is impossible to make the NRM rate of allo-HSCT comparable to those of immune therapies or targeted molecular agents, which might limit the growth potential of allo-HSCT in certain indications (Supplementary Text 12 online).

Based on this major improvement in donor availability and the increase in the numbers of patients in remission, there has been an approximately 5%–30% yearly increase in allo-HSCT activity for acute leukemia and MDS, which takes approximately 70% of all allo-HSCT indications [10,12,13]. This increased allo-HSCT activity has also induced an improvement in overall survival in the specific patient population: with a transplant rate rising from 20% to 50% for adult patients with ALL, the 5-year OS doubled during the last decades [8]. Therefore, we believe that immune therapies will facilitate rather than replace allo-HSCT in acute leukemia and ALL essentially in the near future. When and if active immune therapies, including CAR-T cells, become available for AML, thereby enabling rescue and bridging to transplant, a similar increase in transplant activity for R/R patients will be seen.

Additionally, novel regimens with alternative donors also extended the applications of allo-HSCT for nonmalignant disorders, including aplastic anemia (AA) [15], hemoglobinopathies (such as thalassemia), and inherited disorders of metabolism. The activity of allo-HSCT for nonmalignant disorders doubled in Europe and increased by twentyfold in China during the past decade, accounting for over 10% of total allo-HSCT cases worldwide. Of note, AA has been the third most prevalent indication for transplant in China (approximately 13% of allo-HSCT), in which more than half of patients received HID-HSCT [10,12,13].

The emerging role of immune therapies and targeted molecular agents has resulted in decreasing allo-HSCT activity in specific disease groups; for example, allo-HSCT in chronic myeloid leukemia (CML) has decreased dramatically worldwide in recent decades due to the wide application of tyrosine kinase inhibitors (TKIs) [12]. In contrast to ALL in adults, immune therapies might challenge the role of allo-HSCT in lymphoma and multiple myeloma (MM), which account for 3%–12% of total allo-HSCT activity worldwide [1,10,13]. For example, EBMT reported in 2019 showed that allo-HSCT for CLL decreased by 10.9%, a constant trend over recent years, whereas allo-HSCT for NHL decreased by 4.1%, which accounted for approximately 7.1% of total allo-HSCT activity [10]. The recent results of the ZUMA 7 randomized study comparing the use of CAR-T cells versus conventional therapy, including autologous stem cell transplantation (ASCT), in R/R diffuse large B-cell lymphoma (DLBCL) have shown the superiority of CAR-T cells [16]. Another study demonstrated similar progression-free survival and OS for CAR-T compared with allo-HSCT. Moreover, patients undergoing consolidation with allo-HSCT after anti-PD1 therapy experienced similar OS compared with non-transplanted patients in Hodgkin lymphoma. For R/R MM, CAR-T cells targeting anti-B-cell maturation antigen also demonstrated a high overall response rate, with promising progression-free survival (PFS) and OS rates without HSCT. Therefore, it is uncertain whether transplant activity worldwide would remain relatively stable or decrease in lymphoma and MM, considering the anticipated innovations of immune therapies in the next decade (Supplementary Text 13 online).

Thanks to these developments and improved financial support following economic growth, especially in developing countries with lower transplant rates, allo-HSCT activity has recently continuously increased worldwide, although it remains relatively stable in developed countries [1]. By 2019, the annual number of cases of allo-HSCT was estimated to be over 65,000 worldwide, with a yearly growth rate of 6.8% [1], with 19,798 cases in Europe, 9597 in China, and 9498 in the USA, as reported by local registries [10,12,13]. Although it is not possible that allo-HSCT increases in all the indications, we are confident that total allo-HSCT activity worldwide will continue to experience sustained growth, especially in developing countries for the next decade.

In conclusion, we foresee that targeted molecular agents and immune therapy will complement rather than compete with HSCT in leukemia and that enabling bridging to transplant and maintenance posttransplant with monitoring of MRD will seriously improve the overall patient population outcome. The number of transplants will increase at a time when HID makes it possible to have a donor for almost every patient (Fig. 1).

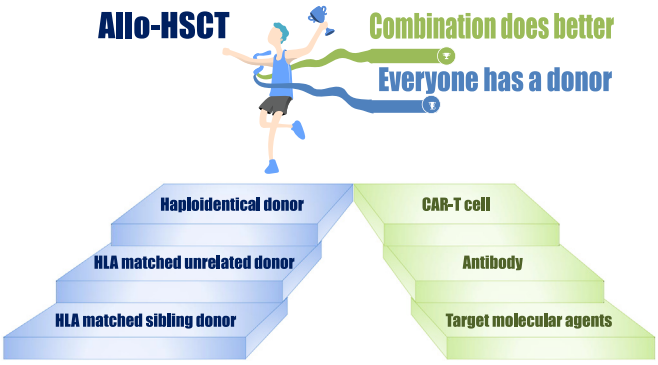

Fig. 1. The triumph of allo-HSCT in the next decade.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary materials

Supplementary materials to this news & views can be found online at https://doi.org/10.1016/j.scib.2022.09.004.

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