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Haploidentical hematopoietic stem cell transplantation without in vitro T-cell-depletion for the treatment of hematologic diseases

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Haploidentical hematopoietic stem cell transplantation (HSCT) has been accepted worldwide as an alternative treatment for patients with hematologic diseases who do not have a human leukocyte antigen (HLA) identical sibling donor or who require urgent transplantation. The results from our nine-year experience showed that granulocyte colony-stimulating factor (G-CSF) primed bone marrow (G-BM) combined with peripheral blood grafts (G-PB) from haploidentical donors, without in vitro T cell depletion (TCD), is a reliable source of stem cells for transplantation to cure acute leukemia and chronic myeloid leukemia. Recent findings confirmed that unmanipulated haploidentical HSCT is a promising protocol that can be successfully extended to treat intermediate and high-risk myelodysplastic syndrome and severe aplastic anemia. Recent observations suggest the association of improved immune recovery with better transplant outcomes after haploidentical HSCT. Chronic graft-vs.-host-disease severity strongly correlates with negative impacts on patients' health-related quality of life, suggesting that it should be successfully controlled.

Keywords: hematopoietic stem cell transplantation, allogeneic, HLA, mismatched, haploidentical

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Haploidentical allogeneic hematopoietic stem cell transplantation (allo-HSCT) is now increasing as a curative therapy for patients with hematologic diseases, who fail to find a suitable unrelated or human leukocyte antigen (HLA)-matched sibling donor. In contrast to $CD34^+$ selected related haplotype transplants,[1] Peking University developed an unmanipulated haploidentical transplantation with granulocyte colony-stimulating factor (G-CSF) primed bone marrow (BM) grafts and peripheral blood grafts (G-PB) as stem cell source. In our nine-year follow-up studies recently published in *Cancer,* 756 patients with leukemia were uniformly treated with haploidentical HSCT without in vitro T cell depletion (TCD) modality.[2] Donor-recipient pairs were assessed for degree of mismatch of HLA-A, B, and DR loci. Results showed that the 3-y leukemia-free survival (LFS) rates were 68% and 49% for patients transplanted in complete remission (CR) or in relapse, respectively. No differences were observed in younger vs. older patients; the somewhat higher 2–4 acute graft-vs.-host-disease (GVHD) incidence for mother-child transplants might be explained by the sex difference of maternal and paternal donors; the effect of the sources of anti-human thymocyte immunoglobulin (ATG) on transplant outcomes could not be evaluated because 98% of the study population received rabbit ATG (Sang Stat) and controlled trials might answer this question. This long-term follow-up study concluded that transplantation of G-PB and G-BM from haploidentical donors by our regimen is reliable for leukemia patients. And more recently, our group reported the results of a prospective study which showed that haploidentical HSCT resulted in lower relapse rate and superior survival compared with chemotherapy alone for acute myeloid leukemia patients with unfavorable cytogenetics in CR.[3] In addition, our recent results showed that allo-HSCT (half of which was haploidentical HSCT),

compared with imatinib, confers significant survival advantages for high- and intermediate-risk patients with accelerated phase chronic myeloid leukemia.[4] Interestingly, Di Bartolomeo P et al.[5] reported a similar results of 80 patients with high risk leukemia who underwent unmanipulated, G-CSF primed BMT from an haploidentical donor. This study at least in part, provides additional support for an opportunity for leukemia patients to benefit from haploidentical HSCT without in vitro TCD.

Apart from leukemia patients, encouraging results with haploidentical HSCT were also achieved with myelodysplastic syndrome (MDS) and severe aplastic anemia (SAA). Chen et al.[6] reported outcomes of 36 patients diagnosed with advanced MDS underwent transplantation from haplo-identical donors without in vitro TCD to confirm that haplo-identical HSCT could be an alternative treatment choice for MDS and patients diagnosed with advanced MDS significantly benefit from receiving HSCT early in their disease course. Moreover, our group has extended unmanipulated haploidentical HSCT to treat non-malignant hematologic disease such as SAA.[7] Reports from recent studies[7,8] suggested that HLA haploidentical HSCT for SAA patients without an HLA-identical sibling donor might be feasible, and a prospective, large-sample, multicenter clinical trial is undertaken to evaluate toxicity and efficacy.

Immune recovery is associated with transplant outcomes.[9] Our recent studies demonstrate that a single measurement of lymphocyte count at day 30 post-transplant is a useful tool for predicting outcomes after unmanipulated haploidentical HSCT in both adult and pediatric patients,[10,11] a finding that adds new support to the idea that early lymphocyte recovery correlates with superior survival in autologous[12] and HLA-identical transplant settings.[13] Furthermore, the recovery of different immune cell subsets after haploidentical HSCT occurs at different rates. Chang et al.[14] found that compared with HLA-matched recipients, haploidentical recipients had lower counts of T cells (particularly CD4 T cells) and dendritic cell (DC) subsets prior to day 90 after transplantation while reconstitution of B cells and monocytes was comparable between the two groups. The prolonged $CD4^+$ T lymphopenia could be related to the higher incidence of cytomegalovirus (CMV) antigenemia in haploidentical recipients, however, the clinical outcomes was not compromised by the early delayed immune reconstitution. Compensatory expansion of monocytes and cytotoxic $CD8^+$ lymphocytes, especially the CTL_{CMV} with the central memory $CD45RO^+$ $CD62L^+$ cell phenotype,[15] may account for the comparable transplant outcomes in terms of survival probabilities following haploidentical and HLA-matched HSCT. Our observations support the need for additional exploration of post-transplant immune-modulation therapy.

Health related quality of life (HRQoL) should be considered to be an important index for evaluating the efficacy of haploidentical HSCT.[16] Our recent retrospective study revealed that compared with the HLA-identical sibling transplant group, patients in the haploidentical group had higher scores in physical functioning, general health, bodily pain, vitality and emotional role functioning, and these patients functioned significantly better on the physical and mental component summaries. Moreover, extensive chronic GVHD has a strongly negative impact on patients' HRQoL, and HLA disparity is not the factor affecting the HRQoL.[17] According to National Institutes of Health consensus criteria for chronic GVHD, HRQoL in patients categorized as having mild and moderate chronic GVHD was significantly better than in those in the severe category.[18] Therefore, severe chronic GVHD should be successfully controlled to improve outcomes. Prospective, multicenter, and large-scale studies are warranted to confirm our results.

To further improve the outcomes after haploidentical HSCT, new methods to decrease the incidence of GVHD and the relapse rates are under investigation. A randomized, controlled, clinical trial concerning risk stratification-directed low-dose glucocorticoid prophylaxis for acute GVHD is undertaken. Patients identified as at high risk of acute GVHD were randomized to receive or not receive low-dose glucocorticoid. Prospective studies with regard to modified donor lymphocyte infusion and interleukin-2 to prevent leukemia relapse are also undergone. As far as donor source is concerned, G-PB alone as allograft from haploidentical donors was also reported to be a promising protocol.[19] Future studies should clarify whether the mixture of G-BM and G-PB or G-PB alone should be chosen as allograft in haploidentical HSCT and identify the better donor choice when more than one donor source was available. Randomized clinical studies should be undertaken to answer these questions. With these improvements, haploidentical HSCT should be included in the treatment algorithm, as a routine practice for patients with hematologic disease who lack a matched donor.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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