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Haplo-BMT: which approach?

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In patients with hematologic malignancies, Di Bartolomeo et al report encouraging outcomes after transplantation of granulocyte-colony stimulating factor (G-CSF)–primed unmanipulated bone marrow from human leukocyte antigen (HLA)–haplotype mismatched (haploidentical) related donors, suggesting that this procedure makes haploidentical transplantation available in all transplant centers.1

Cure of leukemia by allogeneic hematopoietic stem cell transplantation relies on the ability of the immune cells in the graft to recognize and eliminate the leukemia cells (graft-versus-leukemia [GVL] effect). The best donors are HLA-identical siblings because the minor histocompatibility antigen mismatches are associated with low risk of rejection and graft-versus-host disease (GVHD). Because they are available for only about 30% of patients, alternative options include matched unrelated donors, unrelated umbilical cord blood, and full HLA haplotype-mismatched (haploidentical) related donors. Due to HLA incompatibilities, such transplants may be associated with high nonrelapse mortality from diverse combinations of graft rejection, GVHD, and infections. Each alternative source has its own particular advantages and drawbacks (reviewed in Reisner et al2).

Haploidentical transplantation offers the advantages of immediate donor availability for almost all patients and access to donor-derived immune cell therapies after transplantation. Because of multiple class I and II HLA disparities between donor and recipient, major drawbacks are very strong host-versus-graft and graft-versus-host alloresponses leading, respectively, to rejection and GVHD.

In the 1990s such transplants became feasible through the use of high-intensity conditioning regimens and transplantation of a mega-dose of extensively T cell–depleted peripheral blood hematopoietic progenitor cells.2,3 Due to T-cell depletion, major issues were delayed immune reconstitution and high transplant-related/infectious mortality rate especially in adults (whose thymic output is limited) and potential lack of T cell–mediated GVL effect. On the other hand, the posttransplant immune recovery in the absence of any immune suppression created an opportunity for discovering innovative forms of immunotherapy. It favored natural killer (NK)–cell development and revealed donor-versus-recipient NK–cell alloresponses that eradicated acute myeloid leukemia, favored engraftment, protected from GVHD, and improved survival.4 It also allowed effective donor T-cell immunotherapies (devoid of GVHD potential) that protected against infections (reviewed in Reisner et al2). The setting provided evidence that infusion of naturally occurring freshly isolated donor regulatory T cells efficiently protected against otherwise lethal doses of conventional T-cell add-backs given to improve immune reconstitution.5 This Treg/Tcon approach is currently being assessed for its ability to improve immune reconstitution and mediate GVL effects.

In recent years, the haploidentical transplantation field saw the development of non-T cell–depleted (unmanipulated) grafts combined with new strategies to attenuate/modulate donor T-cell alloreactivity and help prevent GVHD, that is, posttransplant high-dose cyclophosphamide,6 posttransplant rapamycin,7 G-CSF–priming of donor bone marrow, and intensified posttransplant immune suppression.8 For example, a low risk of acute and chronic GVHD and encouraging rates of transplant-related mortality were observed in 50 patients with high-risk hematologic malignancies who underwent myeloablative conditioning followed by unmanipulated haploidentical bone marrow transplantation and posttransplantation high-dose cyclophosphamide.9 Likewise, after infusion of unmanipulated grafts, an appreciably low GVHD rate in 45 patients with advanced hematologic malignancies was achieved by exploiting the immune regulatory effect of rapamycin to prevent GVHD (reviewed in Ciceri et al9). In 2009 the Huang group in Beijing first applied G-CSF–priming of unmanipulated haploidentical blood and marrow grafts and intensive posttransplant immune suppression to modulate/down-regulate donor T-cell alloreactivity.8 By applying a modified protocol, Di Bartolomeo et al have achieved promising results in terms of engraftment rate, incidence of GVHD, and survival.1 Key features of their protocol were (1) a chemotherapy-based conditioning regimen, (2) transplantation of only G-CSF–primed bone marrow, and (3) intensified GVHD prophylaxis (anti–thymocyte globulin, cyclosporine, methotrexate, mycophenolate mofetil, and anti–CD25 antibody).

Eighty patients with high-risk hematologic malignancies received transplants; 45 at standard-risk were in complete remission 1 or 2 and 35 at high risk were over complete remission 2 or had active disease. After a median follow-up of 18 months, 39 of 80 patients (49%) were alive in complete remission. The 3-year probabilities of overall and disease-free survival were, respectively, 54% ± 8% and 33% ± 9% for standard-risk patients and 44% ± 8% and 30% ± 9% for high-risk patients. The authors concluded that outcomes were better than reported in the Beijing study because they had used bone marrow alone rather than a combination of bone marrow and peripheral blood cells, and had strengthened GVHD prophylaxis by adding anti–CD25 antibody. Even though they could not assess the impact of their protocol on relapse because of heterogeneity of diagnoses, they suggest their approach is a feasible, valid option. Because it does not need dedicated laboratory facilities and personnel for cell manipulation, they suggest it makes haploidentical transplantation available in all transplant centers.

In conclusion, recent years have witnessed acceptance of, and development of diverse approaches to, haploidentical transplantation. The original approach, transplantation of high numbers of T cell–depleted hematopoietic progenitor cells and no posttransplant immune suppression has, with over 15 years of follow-up, provided well-established outcomes in adults and children and continues to offer unique opportunities for innovative immunotherapeutic strategies. On the other hand, new, unmanipulated graft-based approaches such as that adopted by Di Bartolomeo et al provide promising results that need to be confirmed in longer-term follow-ups. Moreover, they have definitely fostered interest and debate in the field of haploidentical
transplantation and served to substantially extend its use.

At present, a leukemia patient who needs a transplant but has not found a matched donor within the family or the volunteer donor registry has the option of umbilical cord blood or haploidentical transplantation. As retrospective studies have shown no substantial differences in outcomes, the transplant center’s experience currently determines the choice.

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REFERENCES
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