Progress in Hematopoietic Cell Transplantation

This edition of Cancer Control includes an exciting collection of articles that I anticipate will be instructive not only to transplant specialists, but also to readers within a much broader base of hematology and medical oncology. The contributors describe major advances in transplantation technology, disease-specific outcomes, and allied supportive care following allogeneic hematopoietic cell transplantation (HCT).

Given that many potential candidates for allogeneic HCT will not have a matched sibling donor, alternative donor sources — notably including adult matched unrelated donors — have allowed greater access to transplantation. Historically, outcomes following unrelated donor HCT have been relatively inferior to those following matched sibling donor HCT. Importantly, while this impression may influence attitudes regarding access to and referral for transplantation, major progress including advances in high-resolution HLA typing and transplantation technology have led to improved outcomes. Temporal trends demonstrate ongoing improvement in HCT outcomes compared to historical cohorts. In her review, Dr Perez describes current literature that suggests comparable outcomes following matched unrelated donor transplantation and sibling donor transplantation. As demonstrated by several retrospective analyses from single institutions and from the Center for International Blood and Marrow Transplant Research (CIBMTR), survival appears to be comparable across several disease conditions, such as acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL). For those without a suitable matched unrelated donor, other donor options exist, such as umbilical cord blood and mismatched unrelated donors. Efforts to improve outcomes following mismatched unrelated donor HCT have focused on novel strategies to mitigate the risk of severe graft-vs-host disease (GVHD).

Advances in umbilical cord blood transplantation are reviewed in detail in this issue by Dr Brunstein. Utilization of umbilical cord blood as an alternative stem cell donor source has grown dramatically. Beyond filling an unmet need for stem cells in those without a suitably matched related or unrelated donor, current evidence suggests that umbilical cord blood transplantation is a viable option with several distinct advantages, such as rapid availability and potentially decreased risk for GVHD, as well as disadvantages, including delayed engraftment. Single umbilical cord blood transplantation is an established therapy in pediatric transplantation. In adults, double umbilical cord blood transplantation has allowed the delivery of adequate nucleated cell dose and CD34+ cell dose. The greatest body of evidence involves transplantation outcomes following acute leukemia. In this setting, several multi-institutional- and registry-based studies suggest comparable leukemia-free survival following sibling donor, unrelated donor, and double umbilical cord blood transplantation. Most comparative analyses suggest delayed engraftment, increased treatment-related mortality, and increased infectious complications in this setting following umbilical cord blood transplantation. An interesting theme emerging from several reports is that relapse risk may be decreased following umbilical cord blood transplantation. This intriguing finding requires further validation in prospective studies. Other smaller studies indicate that umbilical cord blood transplantation may be effective in other disease conditions including chronic myelogenous leukemia, myelodysplastic syndrome, and lymphoma.

In the following articles, contributors focus on advances in transplantation for specific disease entities, including AML, lymphoma, and multiple myeloma. Dr Hamadani and colleagues first describe the current status of reduced-intensity conditioning and allogeneic HCT for AML. Evidence demonstrates that allogeneic HCT offers superior outcomes for AML with intermediate- and high-risk patients in first complete remissions. However, older adults may suffer intolerable toxicity and death following traditional myeloablative conditioning. Importantly, the authors highlight evidence demonstrating that many patients with AML who have achieved remission with induction chemotherapy are not referred for transplant consultation due to perceptions regarding patient age and comorbidity. An increasing body of evidence suggests that conditioning with reduced-intensity or nonmyeloablative regimens may allow greater access to HCT for such patients. Data suggest that leukemia-free survival approximates that reported previously for myeloablative conditioning for AML in first complete remission. Those with more advanced disease, particularly relapsed/refractory disease, continue to suffer poor outcomes. Novel approaches have aimed to amplify the antitumor activity of the transplant in these settings with staged induction, transplantation, and pre-emptive donor lymphocyte infusion strategies, as well as through the incorporation of radioimmunotherapeutic therapy. Further investigation will guide optimal utilization of reduced-intensity vs myeloablative conditioning. Such a trial will be conducted by the BMT Clinical Trials Network.

Drs Ayala and Tomblyn provide a comprehensive review of indications for and outcomes following autologous
and allogeneic HCT for patients with Hodgkin and non-Hodgkin lymphoma. Autologous HCT has a vital role in therapy of relapsed diffuse large B-cell lymphoma and may prolong progression-free survival as part of initial therapy in high-risk patients. Those with relapsed disease following prior autologous may have successful outcomes with reduced-intensity allogeneic HCT. Allogeneic HCT may cure those with follicular lymphoma, and ongoing efforts aim to limit HCT mortality through the use of reduced-intensity regimens. Consolidative autologous HCT in first remission for mantle cell lymphoma (MCL) appears to improve outcome, and allogeneic HCT has a role in relapsed/refractory MCL, in particular following relapse after prior autologous HCT. Patients with relapsed/refractory Hodgkin lymphoma should be referred for consideration of autologous HCT and reduced-intensity allogeneic HCT following relapse after prior autologous HCT. Evidence also demonstrates safety and successful outcomes for autologous HCT among patients with HIV infection, and ongoing efforts are examining the feasibility of allogeneic HCT in HIV-infected patients. These data all speak to an important role for transplantation therapy in the spectrum of lymphoma care.

Next, Drs Nishihori and Alsina provide a state-of-the-art review on autologous and allogeneic HCT in multiple myeloma. Despite advances in primary therapy and novel approaches to relapsed/refractory disease, multiple myeloma remains largely an incurable condition. Several landmark studies have established the role of high-dose therapy and autologous HCT, and later investigation has aimed to improve on the success of autologous HCT by incorporating novel therapeutic agents and providing consolidation and maintenance therapy after autologous HCT. The potential curative ability of allogeneic HCT has motivated investigators to examine myeloablative and reduced-intensity conditioning approaches followed by allogeneic HCT. Tandem autologous reduced-intensity allogeneic HCT may also provide an effective therapeutic program with moderate toxicity, but major trials comparing tandem autologous HCT to tandem autologous reduced-intensity allogeneic HCT have failed to reach uniform conclusions. Ongoing investigation will help to determine the impact of tandem autologous HCT, consolidation chemotherapy following autologous HCT, and maintenance therapy. Allogeneic HCT should be considered in the context of a clinical trial for patients who have progressive disease after autologous HCT.

In the last article, I provide a comprehensive discussion of acute and chronic GVHD to orient readers to the major considerations in biology, diagnosis, classification, prevention, and therapy of these immune-mediated disorders following allogeneic HCT. Major insights into acute GVHD pathogenesis have led to advances in the prevention and therapy, but challenges remain. Ongoing clinical trials aim to better prevent the syndrome and provide more effective primary therapy, thus avoiding the adverse outcomes associated with advanced, refractory disease. Following a 2005 Chronic GVHD NIH Consensus Conference, we have seen a major resurgence of activity in chronic GVHD research as well as significant proposed changes in the classification and management of the syndrome. The goals of current efforts are to improve our understanding of the pathophysiology of this syndrome, prevent its occurrence after allogeneic HCT, and improve outcome of chronic GVHD therapy. All of these allied efforts are directed toward reducing the impact of these complications on morbidity, mortality, and impaired patient-reported quality of life after HCT.

The underlying theme throughout this edition of Cancer Control is one of ongoing progress and improvements in transplant technology and outcomes. I anticipate that these comprehensive but succinct reviews will not only educate practicing hematologists and medical oncologists on the current status of these important topics, but also encourage providers to discuss transplantation with suitable patients and when appropriate, refer them for transplant consultation.

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