

Bone Marrow Transplantation for Non-Malignant Disease

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Allogeneic hematopoietic stem cell transplantation (HSCT) has long been applied in treatment of non-malignant life-threatening conditions such as severe combined immuno-deficiency (SCID), congenital metabolic disorders, and severe aplastic anemia (SAA) [1]. Although rare diseases, many advances in HSCT have been pioneered in these conditions: HLA-mismatched family donors, unrelated donors, T-cell depletion, mesenchymal cell treatment, umbilical cord transplants, and stem cell gene therapy. While HSCT produces excellent results in SCID [2], there is controversy as to the use of pretransplant chemotherapy to restore full B-cell function. For ADA SCID, correction of both the metabolic and immune defects are critical and recent gene transfers into HSC appear safe and effective when combined with nonmyeloablative conditioning [3]. Other work reveals that marrow mesenchymal cells can correct inherited diseases of cartilage and bone [4]. For individuals with SAA and an HLA-identical sibling, current results of allografting produce cure rates of approximately 90% and current trials explore ways to further reduce the acute and chronic toxicities of the procedure [5].

The balance of risk and gain is especially important in non-malignant conditions with little immediate mortality but considerable chronic morbidity [6]. Thalassemia and sickle cell disease (SCD) represent the most prevalent genetic diseases in the world and ablative conditioning and allogeneic HSCT offer the opportunity for cure; however, challenges reside in patient selection, donor availability, timing and affordability of transplant. For children with class I thalassemia, cure rates of 90% are observed [7]. For older individuals and those with more advanced disease or transfusion sequelae, new approaches are needed. While the clinical phenotype and tempo of SCD are often unpredictable, SCT for young

individuals with advanced, symptomatic disease appears efficacious with about 85% long-term, sickle-free survival [8]. Future research centers on the use of nonablative regimens to create stable mixed donor-host chimerism [9].

Autoimmune diseases have long held interest for the hematologist and this has increased with recent evidence that autoimmune conditions may originate as stem cell disorders and that HSCT may offer effective therapy [10]. Animal models of autoimmunity suggest that in spontaneous (genetic) disease, allografting can prevent disease and reverse organ damage; conversely, in antigenic induction (acquired) disease, myeloablative conditioning and autografting can correct the disorder. At present there is controversy as to patient selection, preparative regimen, use and source of stem cells [11]. Nonetheless, impressive initial phase II study results underscore the need for controlled clinical trials to properly evaluate the risks and benefits of HSCT [12].

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