Hematopoietic Stem Cell Transplantation for Severe Combined Immune Deficiency or What the Children have Taught Us

Joel M. Rappeport, MD[a], Richard J. O'Reilly, MD[b,c,d], Neena Kapoor, MD[e,f], Robertson Parkman, MD[g,h,*]

KEYWORDS

- Severe combined immune deficiency
- Hematopoietic stem cell transplantation • Unrelated • In utero
- Gene transfer

A version of this article was previously published in the *Immunology and Allergy Clinics of North America*, 30:1.

This work was supported by Grant Nos. CA100265 and HL54850 from the National Institutes of Health.

[a] Department of Internal Medicine, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA

[b] Department of Pediatrics, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Box 139, New York, NY 10021, USA

[c] Pediatric Bone Marrow Transplant Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

[d] Pediatric Oncology Research, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[e] Department of Pediatrics, University of Southern California Keck School of Medicine, Los Angeles, CA, USA

[f] Bone Marrow Transplantation Program, Division of Research Immunology/Bone Marrow Transplantation, Childrens Hospital Los Angeles, Los Angeles, 4650 Sunset Boulevard, Mail Stop 62, Los Angeles, CA 90027, USA

[g] Division of Research Immunology/BMT, and The Saban Research Institute, Childrens Hospital Los Angeles, 4650 Sunset Boulevard, Mail Stop 62, Los Angeles, CA 90027, USA

[h] Department of Pediatrics, Molecular Microbiology and Immunology, University of Southern California Keck School of Medicine, Los Angeles, CA, USA

* Corresponding author. Division of Research Immunology/BMT, and The Saban Research Institute, Childrens Hospital Los Angeles, 4650 Sunset Boulevard, Mail Stop 62, Los Angeles, CA 90027.

E-mail address: rparkman@chla.usc.edu

Hematol Oncol Clin N Am 25 (2011) 17–30
doi:10.1016/j.hoc.2010.11.002 **hemonc.theclinics.com**
0889-8588/11/$ – see front matter

More than 40 years ago, the first successful allogeneic hematopoietic stem cell transplantation (HSCT) was reported by Robert A. Good, MD and his colleagues[1] for a child with severe combined immunodeficiency (SCID). In the succeeding years, HSCT for SCID patients have represented only a small portion of the total number of allogeneic HSCT performed. Nevertheless, the clinical and biologic importance of the patients transplanted for SCID has continued. SCID patients were the first to be successfully transplanted with nonsibling related bone marrow, unrelated bone marrow, T-cell depleted HSCT, and genetically corrected (gene transfer) autologous HSC.[2–5] In addition, many of the biologic insights that are now widely applied to allogeneic HSCT were first identified in the transplantation of SCID patients. Therefore, this article reviews the clinical and biologic lessons that have been learned from HSCT for SCID patients, and how the information has impacted the general field of allogeneic HSCT.

PRELUDES

In 1956 it was established that rodents receiving total body irradiation (TBI) could be rescued from the lethality of bone marrow failure by the infusion of histocompatible bone marrow.[6] In those studies the importance of histocompatibility for the successful rescue of the animals from lethal TBI by the prevention of graft-versus-host disease (GVHD) was identified. In the decade between the biologic reality that the transplantation of bone marrow could rescue irradiated animals and the first successful human allogeneic HSCT, clinical investigators attempted to apply the biologic principles to the treatment of patients. A sentinel event was the irradiation accident that occurred in Yugoslavia in 1959 where 6 patients, who were heavily irradiated, were subsequently treated by the infusion of either fetal liver and spleen cells or unrelated bone marrow cells.[7] No sustained donor hematopoietic engraftment was seen in any patients, although slight increases in donor-type erythrocytes were transiently seen in some patients. The patient with the highest dose of irradiation died whereas the other patients had autologous hematopoietic recovery. Other early attempts included the use of high-dose irradiation/chemotherapy and pooled allogeneic bone marrow for the treatment of related and unrelated patients with acute leukemia. Patients with aplastic anemia were infused with bone marrow from identical twins with some patients having hematopoietic improvement, but it was unclear whether their improvement in hematopoiesis was due to the HSCT or the spontaneous recovery of their underlying aplastic anemia. Many allogeneic recipients developed acute GVHD that had similarities to GVHD seen in rodents following histoincompatible transplants. Thus, clinicians were aware that histocompatibility might improve the likelihood of successful HSCT. During the 1960s, the development of serologic reagents to detect human leukocyte antigen (HLA)-A and HLA-B permitted physicians to determine the class I histocompatibility of potential donors and recipients. The development of the mixed lymphocyte culture (MLC) permitted the determination of class II histocompatibility because no antiserum to HLA-DR existed.

CLINICAL ADVANCES

Allogeneic-Related HSCT

The first successful allogeneic HSCT was a member of a kindred in which 11 male infants had died due to severe recurrent infections during the first year of life.[1] At admission, the child had draining skin pustules, no detectable lymph nodes, and lymphopenia. At that time, no phenotypic assays existed for the enumeration of T lymphocytes, but the diagnosis was confirmed by the absence of cutaneous delayed