Leukemia represents the most common pediatric malignancy, accounting for approximately 30% of all cancers in children less than 20 years of age. Most children diagnosed with leukemia are cured without hematopoietic stem cell transplantation (HSCT), but for some high-risk subgroups, allogeneic HSCT plays an important role in their therapeutic approach. The characteristics of these high-risk subgroups and the role of HSCT in childhood leukemias are discussed.

Allogeneic hematopoietic stem cell transplantation from siblings, unrelated donors or HLA mismatched family members has become an important procedure to offer a chance of cure to children and adolescents with acute leukemia at high risk of relapse and those with certain genetic diseases. Bone marrow (BM) was the only stem cell source for many years. During the past 15 years, peripheral blood stem cells from granulocyte colony-stimulating factor (G-CSF) mobilized healthy donors, or umbilical cord blood from related or unrelated donors, have become available. Each stem cell source has different risks/benefits for patients and donors, the choice depending not only on availability, but also on HLA compatibility and urgency of the HSCT. This review will analyze the advantages and limitations of each of these options, and the main criteria which can be applied when choosing the appropriate stem cell source for pediatric transplant recipients with acute leukemia.

Since the 1950s, the overall survival of children with cancer has gone from almost zero to approaching 80%. Although there have been notable successes in treating solid tumors such as Wilms tumor, some childhood solid tumors have continued to elude effective therapy. With the use of mega-therapy techniques such as tandem transplantation, dose escalation has been pushed to the edge of dose-limiting toxicities, and any further improvements in event-free survival will have to be achieved through novel therapeutic approaches. This article reviews the status of autologous and allogeneic hematopoietic stem cell transplantation (HSCT) for many pediatric solid tumor types. Most of the clinical experience in transplant for pediatric solid tumors is in the autologous setting, so some general
principles of autologous HSCT are reviewed. The article then examines
HSCT for diseases such as Hodgkin disease, Ewing sarcoma, and neuro-
blastoma, and the future of cell-based therapies by considering some ex-
perimental approaches to cell therapies.

The Graft-Versus-Tumor Effect in Pediatric Malignancy

Terry J. Fry, Andre Willasch, and Peter Bader

Because severe forms of the graft-versus-host reaction directed against
normal tissues (also termed graft-versus-host disease [GVHD]) also con-
tribute to morbidity and mortality following allogeneic hematopoietic
stem cell transplantation, major efforts have focused on strategies to sep-
rate GVHD from the potentially beneficial immune reactivity against tumor
(also called the graft-versus-tumor [GVT] effect). This article focuses on the
data supporting the contribution of the GVT effect to cure of malignancy,
what is known about the biology of the GVT reaction, and, finally, strate-
gies to manipulate the GVT effect to increase the potency of HSCT.

T-cell-based Therapies for Malignancy and Infection in Childhood

Nabil Ahmed, Helen E. Heslop, and Crystal L. Mackall

One major advance in T-cell-based immunotherapy in the last 20 years has
been the molecular definition of numerous viral and tumor antigens. Adoptive
T-cell transfer has shown definite clinical benefit in the prophylaxis and
treatment of viral infections that develop in pediatric patients after allogene-
ic transplant and in posttransplant lymphoproliferative disease associ-
ated with Epstein-Barr virus. Developing adoptive T-cell therapies for
other malignancies presents additional challenges. This article describes
the recent advances in T-cell-based therapies for malignancy and infection
in childhood and strategies to enhance the effector functions of T cells and
optimize the cellular product, including gene modification and modulation
of the host environment.

Immunotherapy in the Context of Hematopoietic Stem Cell Transplantation: The
Emerging Role of Natural Killer Cells and Mesenchymal Stromal Cells

Arjan C. Lankester, Lynne M. Ball, Peter Lang, and Rupert Handgretinger

Immunotherapy in the context of hematopoietic stem cell transplantation
has been dominated for many years by T-cell- and dendritic-cell-based
treatment modalities. During the last decade, insight into the biology of
natural killer (NK) cells and mesenchymal stromal cells (MSC) has rapidly
increased and resulted in NK- and MSC-based therapeutic strategies in
clinical practice. This article reviews current knowledge of the biology
and clinical aspects of NK cells and MSC.

Current International Perspectives on Hematopoietic Stem Cell Transplantation
for Inherited Metabolic Disorders

Jaap J. Boelens, Vinod K. Prasad, Jakub Tolar, Robert F. Wynn,
and Charles Peters

Inherited metabolic disorders (IMD) or inborn errors of metabolism are a di-
verse group of diseases arising from genetic defects in lysosomal enzymes
or peroxisomal function. These diseases are characterized by devastating systemic processes affecting neurologic and cognitive function, growth and development, and cardiopulmonary status. Onset in infancy or early childhood is typically accompanied by rapid deterioration. Early death is a common outcome. Timely diagnosis and immediate referral to an IMD specialist are essential steps in management of these disorders. Treatment recommendations are based on the disorder, its phenotype including age at onset and rate of progression, severity of clinical signs and symptoms, family values and expectations, and the risks and benefits associated with available therapies such as allogeneic hematopoietic stem cell transplantation (HSCT). This review discusses indications for HSCT and outcomes of HSCT for selected IMD. An international perspective on progress, limitations, and future directions in the field is provided.

**Bone Marrow Transplantation for Inherited Bone Marrow Failure Syndromes**
Parinda Mehta, Franco Locatelli, Jan Stary, and Franklin O. Smith

The inherited bone marrow failure (BMF) syndromes are characterized by impaired hematopoiesis and cancer predisposition. Most inherited BMF syndromes are also associated with a range of congenital anomalies. Progress in improving the outcomes for children with inherited BMF syndromes has been limited by the rarity of these disorders, as well as disease-specific genetic, molecular, cellular, and clinical characteristics that increase the risks of complications associated with hematopoietic stem cell transplantation (HSCT). As a result, the ability to develop innovative transplant approaches to circumvent these problems has been limited. Recent progress has been made, as best evidenced in studies adding fludarabine to the preparative regimen for children undergoing unrelated donor HSCT for Fanconi anemia. The rarity of these diseases coupled with the far more likely incremental improvements that will result from ongoing research will require prospective international clinical trials to improve the outcome for these children.

**Hematopoietic Stem Cell Transplantation for Osteopetrosis**
Colin G. Steward

Osteopetrosis is the generic name for a group of diseases caused by deficient formation or function of osteoclasts, inherited in either autosomal recessive or dominant fashion. Osteopetrosis varies in severity from a disease that may kill infants to an incidental radiological finding in adults. It is increasingly clear that prognosis is governed by which gene is affected, making detailed elucidation of the cause of the disease a critical component of optimal care, including the decision on whether hematopoietic stem cell transplantation is appropriate. This article reviews the characteristics and management of osteopetrosis.

**Hematopoietic Stem Cell Transplantation for Hemoglobinopathies: Current Practice and Emerging Trends**
Frans J. Smiers, Lakshmanan Krishnamurti, and Guido Lucarelli

Despite improvements in the management of thalassemia major and sickle cell disease, treatment complications are frequent and life expectancy
remains diminished for these patients. Hematopoietic stem cell transplantation (HSCT) is the only curative option currently available. Existing results for HSCT in patients with hemoglobinopathy are excellent and still improving. New conditioning regimens are being used to reduce treatment-related toxicity and new donor pools accessed to increase the number of patients who can undergo HSCT.

Bone Marrow Transplantation for Primary Immunodeficiency Diseases 207
Paul Szabolcs, Marina Cavazzana-Calvo, Alain Fischer, and Paul Veys

Advances in immunology have led to a breathtaking expansion of recognized primary immunodeficiency diseases (PID) with over 120 disease-related genes identified. In North America alone more than 1000 children have received allogeneic blood or marrow transplant over the past 30 years, with the majority surviving long term. This review presents results and highlights challenges and notable advances, including novel less toxic conditioning regimens, to transplant the more common and severe forms of PID. HLA-matched sibling donors remain the ideal option, however, advances in living donor unrelated HSCT and banked umbilical cord blood grafts provide hope for all children with severe PID.

Autologous Hematopoietic Stem Cell Transplantation for Childhood Autoimmune Disease 239
Francesca Milanetti, Mario Abinun, Julio C. Voltarelli, and Richard K. Burt

Autologous and allogeneic hematopoietic stem cell transplantation (HSCT) can be used in the management of patients with autoimmune disorders. Experience gained in adults has helped to better define the conditioning regimens required and appropriate selection of patients who are most likely to benefit from autologous HSCT. The field has been shifting toward the use of safer and less intense nonmyeloablative regimens used earlier in the disease course before patients accumulate extensive irreversible organ damage. This article reviews the experience of using autologous HSCT in treating the most common childhood autoimmune and rheumatic diseases, primarily juvenile idiopathic arthritis, systemic lupus erythematosus, and diabetes mellitus.

Management of Acute Graft-Versus-Host Disease in Children 273
Paul A. Carpenter and Margaret L. MacMillan

Acute graft-versus-host disease (aGVHD) remains a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT) in children. Although 30% to 50% of children respond to corticosteroids as initial therapy, the optimal initial or second-line therapies have not yet been determined. Newer approaches with combination therapy, novel agents, monoclonal antibodies, and/or cellular therapies show some promise but require prospective well-designed trials that include children to establish their efficacy. This article reviews the clinical presentation, treatment, and practical management guidelines for children with aGVHD.
Chronic Graft-Versus-Host Disease (GVHD) in Children
Kristin Baird, Kenneth Cooke, and Kirk R. Schultz

Five-year survival rates for childhood cancer now exceed 80% and with the significant progress made by the transplant community in developing less toxic conditioning regimens and in the treatment of posttransplant complications, allo-hematopoietic stem cell transplantation (HSCT) contributes significantly to that population of long-term survivors. In this context, the acute and long-term toxicities of chronic graft-versus-host disease (cGVHD) have an ever-increasing effect on organ function, quality of life, and survival; patients and families who initially felt great relief to be cured from the primary disease, now face the challenge of a chronic debilitating illness for which preventative and treatment strategies are suboptimal. Hence, the development of novel strategies that reduce and/or control cGVHD, preserve graft-versus-tumor effects, facilitate engraftment and immune reconstitution, and enhance survival after allo-HSCT represents one of the most significant challenges facing physician-scientists and patients.

The Burden of Cure: Long-term Side Effects Following Hematopoietic Stem Cell Transplantation (HSCT) in Children
K. Scott Baker, Dorine Bresters, and Jane E. Sande

Children who survive hematopoietic stem cell transplantation (HSCT) are at risk for an inordinate number of long-term side effects. Late effects can be secondary to the underlying diagnosis for which the transplant is performed, prior treatment of the disease, the transplant preparative regimen, treatment of the complications of transplant, and immunologic interactions between the graft and the host. This article describes the risks and manifestations of the most commonly reported late effects in survivors of pediatric HSCT.

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