ASBMT American Society for Blood and Marrow Transplantation

REVIEW

# Advancement of Pediatric Blood and Marrow Transplantation Research in North America: Priorities of the Pediatric Blood and Marrow Transplant Consortium

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Advances in pediatric bone marrow transplantation (BMT) are slowed by the small number of patients with a given disease who undergo transplantation, a lack of sufficient infrastructure to run early-phase oncology protocols and studies of rare nonmalignant disorders, and challenges associated with funding multi-institutional trials. Leadership of the Pediatric Blood and Marrow Transplant Consortium (PBMTC), a large pediatric BMT clinical trials network representing 77 active and 45 affiliated centers worldwide, met in April 2009 to develop strategic plans to address these issues. Key barriers, including infrastructure development and funding, along with scientific initiatives in malignant and nonmalignant disorders, cellular therapeutics, graft-versus-host disease, and supportive care were discussed. The PBMTC's agenda for approaching these issues will result in infrastructure and trials specific to pediatrics that will run through the PBMTC or its partners, the Blood and Marrow Transplant Clinical Trials Network and the Children's Oncology Group.

*Biol Blood Marrow Transplant 16: 1212-1221 (2010) © 2010 American Society for Blood and Marrow Transplantation*

**KEY WORDS:** Hematopoietic Stem Cell Transplantation, Pediatrics, Transplantation of Non-malignant Disorders, Cooperative Group Studies

## INTRODUCTION

The field of pediatric bone marrow transplantation (BMT) has long been challenged by the fact that pediatric transplantations are performed for a diverse group of relatively rare disorders. Accepted BMT indications in the pediatric population include 8 different hematopoietic malignancies, themselves uncommon, and at least another 20 even less-common nonmalignant diseases. Because the largest pediatric BMT centers perform only between 50 and 100 transplantations yearly, even high-volume centers do only

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*Financial disclosure:* See Acknowledgments on page 1219.

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Received November 5, 2009; accepted December 30, 2009



1083-8791/$36.00
doi:10.1016/j.bbmt.2009.12.536

**Table 1. Recent Pediatric BMT Trials Developed by PBMTC or Jointly by PBMTC Working with Other Cooperative Groups**

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| COG ASCT0431/PBMTC ONC051: A Randomized Trial of Sirolimus-Based Graft-versus-Host Disease Prophylaxis after Hematopoietic Stem Cell Transplantation in Selected Patients with CR1 and CR2 ALL |
| COG ASCT0521/ PBMTC SUP051: Soluble Tumor Necrosis Factor Receptor: Enbrel (Etanercept) for the Treatment of Acute Noninfectious Pulmonary Dysfunction (Idiopathic Pneumonia Syndrome) following Allogeneic Stem Cell Transplantation |
| COG ASCT0631/PBMTC STC051: A Phase III Randomized Trial of G-CSF–Stimulated Bone Marrow versus Conventional Bone Marrow as a Stem Cell Source In Matched Sibling Donor Transplantation |
| BMT CTN 0601: Unrelated Donor Hematopoietic Cell Transplantation for Children with Severe Sickle Cell Disease Using a Reduced-Intensity Conditioning Regimen. |
| PBMTC NMD0901: A Pilot Trial of Unrelated Donor Hematopoietic Cell Transplantation for Children with Severe Thalassemia Using a Reduced-Intensity Conditioning Regimen, with the Thalassemia Trials Network |

BMT indicates bone marrow transplant; PBMTC, Pediatric Blood and Marrow Transplant Consortium; COG, Children's Oncology Group; BMT CTN, The Blood and Marrow Transplant Clinical Trials Network; ASCT, allogeneic stem cell transplant.

a handful of transplantations each year for any specific indication. The fact that meaningful clinical research requires collaborative, multi-institutional studies with a large number of relatively small centers is becoming increasingly apparent.

Over the past few years, efforts by 3 large cooperative groups in North America and Australia—the Children's Oncology Group (COG), the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) and the Pediatric Blood and Marrow Transplant Consortium (PBMTC)—have resulted in the planning and implementation of a series of multicenter pediatric transplantation trials (Table 1). The COG conducts cancer-related BMT trials in children, and the BMT CTN conducts adult and pediatric multicenter trials addressing all aspects of the transplantation experience. Both groups focus on large phase II and III trials. The BMT CTN is committed to developing selected larger trials in malignant and nonmalignant pediatric conditions and is currently conducting a phase II trial evaluating transplantation in children with sickle cell disease; however, its commitment to larger trials means that ideas requiring small pilot studies generally are not considered in its scientific agenda. Pilot data are needed when considering larger trials, but these data are lacking for many issues related to pediatric BMT, including transplantation strategies for both malignant and nonmalignant disorders.

Comprising 77 full-member pediatric centers in North America, Australia, and New Zealand, the PBMTC is the largest clinical trials group focused exclusively on BMT in children and adolescents. The PBMTC works closely with both the COG and the BMT CTN. Most PBMTC centers participate in COG trials, and many PBMTC investigators are involved in COG Hematopoietic Stem Cell Transplantation (HSCT) Committee leadership and COG study development. This facilitates transition of successful PBMTC pilot trials focused on cancer into larger COG trials. The BMT CTN comprises 16 core centers, 13 of which are large transplantation centers with both adult and pediatric programs, 2 of which are small consortia, and the remaining core center is the PBMTC. As mentioned earlier, pediatric transplantation indications are rare, and including the PBMTC as a core center of the BMT CTN provides the opportunity to participate in BMT CTN studies for more than 60 additional pediatric centers who are not part of other core centers. This is important, because successful pediatric HSCT trials often require at least 30-40 centers because of the rarity of the diseases for which transplantation is performed. Because the PBMTC is a core center, the PBMTC chair sits on the BMT CTN steering committee, and PBMTC leadership participate in BMT CTN committees and leadership. In addition, PBMTC members can propose trials for consideration by the BMT CTN steering committee.

As alluded to earlier, the PBMTC has assumed a role in developing novel, early-phase trials that can provide necessary preliminary data for larger COG and BMT CTN trials. The PBMTC is the only large cooperative group committed to studying many rare conditions in which phase III trials are not possible. BMT to treat these orphan diseases can be advanced only by smaller studies performed by a large group, such as the PBMTC. The PBMTC has developed the necessary infrastructure to develop both pilot studies and broad-based trials addressing the treatment of rare orphan diseases by BMT with a grant from the St Baldrick's Foundation, a charitable organization dedicated to fighting childhood cancer. A formal collaboration agreement was established in 2009 between the PBMTC and the clinical trial arm of the Center for International Blood and Marrow Transplant Research (CIBMTR), the Resource for Clinical Investigations in Blood and Marrow Transplantation (RCI-BMT). This collaboration included development of a high-quality, good clinical practice–compliant clinical trials infrastructure that uses the data and trials management resources and expertise of the CIBMTR.

Both the PBMTC and the CIBMTR perform studies involving centers in countries worldwide. The PBMTC operations center is part of the National Children's Cancer Foundation (the charitable arm and financial operations center of the COG). This organization performs contracts with COG-affiliated centers around the world, and this expertise is used by the PBMTC. The long-standing PBMTC membership of transplantation groups from Canada, Australia,

and New Zealand has resulted in established methods for institutional ethics board review and data quality assurance. The CIBMTR/National Marrow Donor Program (NMDP) has established contractual relationships with PBMTC centers inside and outside the United States, simplifying data-transfer arrangements. Trials proposed by members are developed and prioritized through a subcommittee structure (see later). Developed protocols undergo review through the PBMTC Scientific Review Committee, with a nonbinding review by the RCI-BMT's Scientific Advisory Committee. Final study approval is provided through a vote of the PBMTC Executive Committee, a body elected by PBMTC members. Studies are funded by the St Baldrick's Foundation, individual governmental and nongovernmental research grants, and industry sponsorship.

In April 2009, A PBMTC strategic planning meeting was held in Vancouver, Canada, that included senior PBMTC and COG transplantation leadership and chairs and vice-chairs of PBMTC subcommittees in nonmalignant disorders, oncologic disorders, stem cell sources/cellular therapeutics, graft-versus-host disease (GVHD), and supportive care. In addition, representatives from the RCI BMT, the National Heart, Lung, and Blood Institute (NHLBI), the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases (NIAID), and the St Baldrick's Foundation participated in the discussions, with each group sharing its research agenda. The meeting focused on defining knowledge gaps and study opportunities in the 5 broad strategy areas mentioned earlier. The meeting concluded with the development of research priorities along with strategies for infrastructure development and funding for pediatric BMT. Priorities in the 5 areas addressed by PBMTC subcommittees are outlined in the next section.

## ALLOGENEIC TRANSPLANTATION FOR NONMALIGNANT PEDIATRIC DISORDERS: CURRENT EFFORTS, STUDY OPPORTUNITIES, AND PRIORITIES

Nonmalignant diseases treated by BMT represent a wide array of diverse disorders, and include approximately 35% of pediatric patients undergoing BMT at PBMTC member institutions. Recognizing that each of these disorders is rare, PBMTC investigators seek to develop feasible national protocols, using the accrual power of the consortium, to address the most pressing clinical questions that may improve the treatment of children with these disorders. Although some disorders involve unique issues that are most effectively addressed by disease-specific protocols, others share common challenges allowing for multi-disease protocols. The PBMTC has developed collaborations with established disease-specific networks when possible and initiated trials to fill unmet needs. Five major categories of nonmalignant disorders are treatable by BMT: (1) hemoglobinopathies, (2) immune deficiency and dysregulation disorders, (3) metabolic storage diseases, (4) BM failure syndromes, and (5) a group of individually unique disorders, such as the leukodystrophies and osteopetrosis. Novel indications for BMT, such as autoimmune illness, and the use of other cellular therapeutic approaches to treat these and other diseases are also part of the nonmalignant disorders group.

What are the pressing clinical challenges in BMT for nonmalignant disorders? First, although matched sibling transplantation using myeloablative (MA) approaches is well established for many nonmalignant disorders, treatment-related mortality (TRM) and GVHD-associated morbidity remains high with unrelated donor (URD) BMT [1,2]. Reduced-intensity conditioning (RIC) regimens hold the promise of decreasing TRM in these disorders, but graft rejection has limited the widespread application of this approach [3]. PBMTC investigators have developed a novel RIC approach that has been adopted by the BMT CTN as a URD transplantation protocol for sickle cell anemia (BMT CTN 0601; Tables 1 and 2) [4]. In addition, the PBMTC has launched a similar trial for thalassemia in cooperation with the Thalassemia Clinical Research Network (TCRN-PBMTC NMD091). PBMTC investigators are collaborating with the BMT CTN to develop a trial of a novel RIC transplantation regimen to treat the immune regulation disorder hemophagocytic lymphohistiocytosis. Continuing efforts to develop regimens that ensure engraftment in nonmalignant disorders while limiting TRM and GVHD will remain a top priority over the next several years.

A second major clinical challenge in nonmalignant BMT is the lack of understanding of outcomes and a consensus approach to BMT for immunodeficiency disorders, especially severe combined immune deficiency (SCID) [5]. In the past, most transplantations for these disorders were done at a limited number of large centers. Today, however, a large number of smaller centers are performing BMT in these children. Because of the ability to engraft T cells with minimal preparation in many of these children, approaches vary dramatically, ranging from simple infusions of T cell–depleted maternal haploidentical grafts without a preparatory regimen to MA approaches for all patients [6]. The PBMTC is working cooperatively as a participant in the Primary Immune Deficiency Treatment Consortium (PIDTC), which recently was awarded an NIAID/Office of Rare Diseases (ORD) U54 grant to study survival and immunologic outcomes, both retrospectively and prospectively, in these patients. PBMTC investigators feel that a key initiative in the coming years will be to design

**Table 2. Hypotheses and Study Priorities in BMT for Nonmalignant Pediatric Disorders**

| Disease | Hypotheses | Current Study/Strategy |
|---|---|---|
| Hemoglobinopathies: | Expand donor pool to URD | BMT CTN 0601 |
| Sickle cell disease, thalassemia | Reduced intensity = less TRM, late effects | PBMTC NMD0901 |
| Hemophagocytic lymphohistiocytosis | Decreased inflammatory response, less TRM with reduced-intensity regimen | PBMTC joint with BMT CTN committee: U34 submitted |
| Immune deficiencies | | |
| SCID | Long-term outcomes of current approaches unknown | Outcomes: retrospective and prospective through PIDTC U54 |
| SCID | Achievement of B cell and T cell with high stem cell/dose plus reduced-intensity regimen | PBMTC study committee/planned grant effort |
| Metabolic storage diseases | Neurocognitive outcomes differ with disease/stem cell source/age; standardization of outcome measures is needed | PBMTC/Hunter's Hope/Lysosomal Disease Network U54 grant joint effort |
| Bone marrow failure | | |
| SAA | Decrease rejection of cord blood; expand donor pool | PBMTC study committee/grant submitted |

BMT indicates bone marrow transplant; PBMTC, Pediatric Blood and Marrow Transplant Consortium; COG, Children's Oncology Group; BMT CTN, The Blood and Marrow Transplant Clinical Trials Network; TRM, treatment related mortality; SCID, severe combined immune deficiency; PIDTC, Primary Immune Deficiency Treatment Consortium; URD, unrelated donor, SAA, severe aplastic anemia.

therapeutic trials based on data gathered by the PIDTC, with a primary aim of establishing both T cell and B cell immune competence using both related donor and URD stem cell sources.

A PBMTC protocol team is working with the Hunter's Hope Foundation and a U54-funded team from the Lysosomal Disease Network (LDN) to develop (1) an initiative aiming to standardize evaluation of the neurocognitive outcomes of children who have previously undergone BMT, and (2) a prospective therapeutic transplantation study for selected metabolic disorders. A key opportunity for studying BMT for metabolic storage diseases is provided by newborn screening for these diseases in several states [7]. Identification of younger high-risk children with some of these diseases may allow BMT at an earlier time point, limiting neurologic damage and possibly improving outcomes. Questions regarding the impact of genotype/phenotype analysis of specific mutations will assist in identifying individuals with severe or milder phenotypes, guiding the use of BMT versus enzyme-replacement strategies.

Finally, although umbilical cord blood (UCB) transplantation is done routinely for many malignant and nonmalignant disorders, high rates of rejection and TRM have limited the use of this stem cell source for BMT in children with severe aplastic anemia (SAA) who have failed immunosuppressive therapy [8]. Recent data generated by PBMTC investigators provide the basis for a current initiative to develop an innovative RIC approach to allow the use of UCB in this population [9]. To date, BMT has been most effective in this group only when a fully HLA-matched URD is available (approximately 30%-40% of the time). Because UCB BMT can succeed with less-stringent HLA matching, improving UCB outcomes in SAA could allow more than 90% of children with this disorder who fail immunosuppression a chance at curative therapy.

In summary, PBMTC initiatives to improve outcomes after BMT for nonmalignant disorders include targeted efforts to (1) establish long-term engraftment of URD sources using safer reduced-intensity approaches, (2) ensure T cell and B cell engraftment and functional immunity after BMT in patients with SCID, (3) standardize assessment of and learn more about neurologic outcomes after transplantation of selected metabolic storage diseases to establish the timing and appropriateness of BMT, and (4) establish approaches that result in high rates of engraftment and survival using UCB for patients with SAA who have failed immunosuppressive therapy (Table 2).

## BLOOD AND MARROW TRANSPLANTATION FOR PEDIATRIC MALIGNANT DISORDERS

Approximately 65%-70% of BMTs in children are performed for high-risk malignancies. MA approaches to BMT deliver maximal treatment intensity and allogeneic BMT approaches deliver immunotherapy through a graft-versus-malignancy effect. But, despite this intense approach, relapse remains the major cause of death in children undergoing BMT for malignancy. With that in mind, the major focus of the PBMTC Oncology Strategy Group is prevention of relapse. Understanding the mechanisms of relapse after BMT is critical for designing more effective and selective BMT therapy. Relapse after BMT implies the existence of mechanisms of chemoresistance, radioresistance, and immunoresistance. The presence of detectable minimal residual disease at the time of the pretransplantation workup is associated with an increased risk of relapse [10,11]. Possible mechanisms to explain this observation include a threshold effect, with an unfavorable effector-to-target ratio; a dose phenomenon that alters the immunologic response; active induction of tolerance by malignant cells;

suppression of immune responses by malignant cells; lack of immunogenicity in malignant cells; loss of target antigens by malignant cells; exhaustion of effector clones; or inadequate T cell function against malignant clones.

Two strategies to reduce the risk of relapse after allogeneic BMT are to administer agents that increase cancer cell susceptibility to immune approaches (ie, induction of apoptosis) and to increase the effectiveness of the BMT in treating the malignant clone. One way to affect cancer cell susceptibility is to administer mTOR inhibitors, such as sirolimus, which induce apoptosis. Sirolimus has both antitumor and immunosuppressive properties and is currently being studied in a phase III COG/PBMTC study (ASCT0431/PBMTC ONC051), with a hypothesis that its antileukemic and proapoptotic effect will decrease relapse posttransplantation for children with acute lymphoblastic leukemia (ALL) [12]. Targeted therapies with side effect profiles compatible with posttransplantation administration, such as tyrosine kinase inhibitors (TKIs; eg, imatinib mesylate), may take minimal residual disease below an immunologic threshold posttransplantation, reducing relapse. In addition, TKIs have been shown to have a number of immunologic effects, working synergistically with donor lymphocyte infusions [13]. A top priority of the oncology strategy group will be further testing of targeted agents and immunotherapeutic strategies (see Cellular Therapeutics) to prevent relapse in the very-high-risk patients undergoing allogeneic and autologous BMT. In addition, whereas the role of BMT as active immunotherapy is well established in hematologic malignancies, the role of alloimmunity in treating chemorefractory pediatric solid tumors is currently being explored. Efforts to improve the efficacy of BMT or immunotherapeutic approaches to refractory solid tumors merit continued attention.

Finally, an important issue after BMT in growing, developing children is the challenge of late effects, including infertility, endocrine issues, and second malignancies. The PBMTC has made significant contributions to defining the role of RIC transplantation in pediatric hematologic malignancies [12]. Continued efforts to define novel approaches to reduce toxicity and decrease late effects, while preserving anticancer efficacy, will remain a priority.

In summary, future efforts to improve outcomes after BMT for malignant disorders should focus on prevention of relapse through (1) manipulation or enhancement of alloimmunity after transplantation, (2) use of peritransplantation cellular therapy or immunotherapy, and (3) use of relevant molecularly targeted therapies that can be administered in the peritransplantation period. In addition, further exploration of the appropriate role of RIC approaches for pediatric malignancies is warranted.

## STEM CELL SOURCES AND CELLULAR THERAPEUTIC APPROACHES IN PEDIATRICS

An ideal stem cell source provides early myeloid and lymphoid engraftment without excessive GVHD. To achieve this goal, the PBMTC conducted a pilot trial using granulocyte colony-stimulating factor (G-CSF)-primed BM for children undergoing transplantation from related donors [14]. The graft content of G-CSF–primed BM included high doses of $CD34^+$ cells with low $CD3^+$ doses compared with peripheral blood stem cells, resulting in rapid engraftment and low rates of chronic GVHD (cGVHD). The study provided preliminary data for an ongoing, jointly developed (PBMTC/COG) phase III trial running through the COG (ASCT0631; Table 1). An important question in alternative donor sources is how the use of 1 or 2 UCB units affects transplantation outcomes. The PBMTC is participating in BMT CTN 0501, a study of single UCB versus double UCB transplantation in pediatric malignancies, testing whether or not a second cord leads to less relapse because of added immunogenicity. These studies will add to a large body of work compiled over the past decade that has defined high-quality stem cell sources for the large majority of patients requiring BMT.

To further improve outcomes using these stem cell sources, the next generation of studies in this area will involve manipulation cells within a graft to improve engraftment, decrease GVHD, or enhance the antimalignancy effect. Although all forms of BMT are "cellular therapy," our use of the term includes manipulations and enhancement of grafts or generation of cellular products from nongraft sources. There are 2 broad approaches to performing cellular therapy in the context of BMT [15]. One approach involves using autologous cells that have been manipulated to better target the patient's cancer and strengthen the patient's immune response. A tumor has escaped the body's immune surveillance, and overcoming this immunologic resistance can be challenging; however, autologous cells can live longer and can maintain immune surveillance if stimulated appropriately, and thus they carry a lower risk of untoward reactions, such as GVHD. A second approach involves using allogeneic cells, which have the capacity for more potent antitumor activity. Modified allogeneic cells can be used before transplantation to increase the depth of a remission, or as part of the BMT or posttransplantation to decrease the risk of relapse or GVHD. Although immunoresistance is the primary challenge in the application of autologous cells, alloimmune-mediated morbidity (eg, GVHD, organ damage) will remain a challenge with the use of allogeneic approaches.

PBMTC centers are pursuing various immunologic and cellular therapeutic approaches to decrease relapse. The infusion of antigen-specific T cells in

children with cancer is appealing, because cellular immunotherapy offers an approach to treating malignancies that may avoid the long-term toxicities associated with conventional cytotoxic chemotherapy and radiation therapy. Current studies on reconstituting or augmenting cellular immunity through the infusion of T cells are limited to single-center or small group studies because of a number of barriers [16].

The major challenges in pursuing adoptive cellular therapies in children are the current lack of significant funding for such trials and the daunting regulatory burden associated with conceiving and executing such therapies in a multicenter setting. The PBMTC cellular therapy strategy group is committed to evaluating cellular therapies in a multicenter setting. The most pressing initial challenge is to establish the regulatory infrastructure within the PBMTC necessary to conduct and monitor such multicenter trials. The feasibility and safety of shipping cells between centers and incorporating such therapies with current therapies must be studied, and issues regarding limiting indemnification of the sponsoring institution must be resolved. We believe that important advances in curing high-risk malignant diseases will involve directed adoptive cellular therapies.

In summary, PBMTC efforts in cellular therapy will start with the testing of promising approaches in a limited-center setting. Once feasibility is established, we will expand these cellular approaches into larger multicenter studies.

## KEY ISSUES IN PEDIATRIC GVHD

Young children differ from others in their rate of GVHD and their ability to recover from GVHD, likely because of thymic activity in the first decades of life. Differences in drug metabolism and the challenges of administering some GVHD therapies to younger children add to the complexity. Only studies that take these distinct differences in young children into account will be able to define optimal GVHD therapy for this group [17].

GVHD remains the major complication of allogeneic BMT. Approaches to improving treatment have focused on biomarkers that can predict the development of GVHD or provide a better understanding of which therapies work best. The PBMTC has assessed both mechanisms and biomarkers associated with the development of GVHD and tested novel therapies for acute GVHD (aGVHD) and cGVHD. Approaches that augment treatment in all patients diagnosed with aGVHD can lead to overtreatment of some patients and worse outcomes because of increased relapse, along with infectious mortality [18]. Thus, identification of patients at high risk for developing aGVHD could lead to individualized treatment approaches based on the risk for GVHD. The PBMTC conducted a study of cytokine gene polymorphisms in 185 children undergoing 6/6 matched URD transplantations at 28 institutions. A significant relationship was observed between tumor necrosis factor-$\alpha$ genotypes and haplotype and the risk of aGVHD [19]. We are currently evaluating the relationship between other gene polymorphisms and posttransplantation outcomes. A major goal of the PBMTC over the next few years will be to prospectively validate multiple biomarkers (eg, proteomic, RNA-based studies of genetic alterations before GVHD) in the pediatric HSCT setting. These results, combined with our cytokine polymorphism study outcomes, will result in identification of patients who are at high risk for GVHD and thus may benefit from augmented immunosuppression.

The PBMTC recently completed accrual of 51 children from 24 institutions onto a phase II study evaluating the safety and efficacy of pentostatin in refractory cGVHD. The drug was well tolerated, and the overall response was 53% [20]. A small group of PBMTC centers will conduct a limited-institution phase I study to examine the toxicity of the CellEx photopheresis machine in children with refractory cGVHD. This study will explore the feasibility of extracorporeal photochemotherapy apheresis in very young children using newer-generation machines better able to serve "small-volume" young children.

In summary, future GVHD studies should focus on validating biomarkers and performing trials of specific agents and approaches that will help us better understand and respond to the unique therapeutic needs and immunologic and physiological differences of young children.

## SUPPORTIVE CARE CHALLENGES IN PEDIATRIC BMT

Supportive care practices comprise a panoply of medical interventions aimed at improving the outcome of BMT. Over the past 2 decades, improvements in supportive care have been a key factor in the significant decrease in TRM associated with both autologous and allogeneic BMT. Of note, although outcomes have improved, centers vary widely in their use of supportive care practices, such as antibacterial prophylaxis or treatment, antifungal prophylaxis and treatment, viral monitoring, nutritional support, and menstrual suppression. Well-designed trials may contribute to the standardization and improvement of supportive care practices. Two pertinent examples from the PBMTC supportive care group include a phase III study demonstrating the utility of oral glutamine in preventing mucositis [21] and a recently completed phase I trial of palifermin in children.

We consider 2 areas of supportive care to be of high priority in children. First, the use of total body

**Table 3. PBMTC Key Priorities for Pediatric BMT**

1. Develop preparative approaches using URD grafts that offer long-term engraftment, reduced toxicity, and reduced GVHD for nonmalignant disorders.
2. Develop safer approaches to BMT for patients with SCID that allow consistent establishment of long-term, functional B cell and T cell immunity using related and URD sources.
3. Study neurocognitive outcomes after BMT for metabolic storage diseases, and develop prospective trials aimed at improving the safety and efficacy of BMT in this population.
4. Develop approaches that allow high levels of successful engraftment in patients with SAA failing immune suppression using unrelated cord blood.
5. Decrease relapse after BMT for malignant disorders by (1) manipulation or enhancement of alloimmunity, (2) use of peritransplantation cellular therapy, or (3) use of peritransplantation targeted therapies.
6. Further explore the appropriate role of reduced-intensity approaches for selected pediatric malignancies.
7. Pilot-test promising cellular therapy approaches in a limited-center setting, followed by expansion into larger multicenter studies. This includes overcoming infrastructure, regulatory, investigational new drug (IND) issues, and funding challenges.
8. Validate biomarkers in and perform GVHD trials targeted at the specific needs of young children.
9. Study the neurocognitive impact of TBI and other myeloablative approaches in infants and younger children.
10. Study the significance and impact of new therapies, and therapeutic outcomes of infection with selected viral pathogens in children.

PBMTC indicates Pediatric Blood and Marrow Transplant Consortium; BMT, bone marrow transplant; URD, unrelated donor, SAA, severe aplastic anemia; SCID, severe combined immune deficiency; GVHD, graft-versus-host disease; TBI, total body irradiation.

irradiation (TBI) in very young children has generated considerable debate. There are concerns about the long-term neurocognitive and neuroendocrine sequelae of TBI in children under 2 or 3 years of age. PBMTC data since 2000 reflect marked variations in practice by center: 46% of reported patients with ALL under age 2 years received TBI, with the remaining institutions using a variety of other approaches. There is a paucity of information on this subject, because few studies have targeted this population. Sanders et al. [22] reported that 15 infants who received 13.2-15.75 cGy TBI had a mean full-scale IQ of was 104 $\pm$ 14 at a median age of 4.4 years. Phipps et al. [23], however, described declining IQ scores at 1 and 3 years posttransplantation in children who underwent transplantation before 3 years of age, although the number of patients in this age group was insufficient to determine whether TBI had a greater impact than non-TBI regimens. These findings were called into question in a subsequent report by the same group [24]. Because TBI-based regimens offer a survival benefit for older recipients with high-risk ALL [25], understanding the developmental implications of this therapy on infants is important. The PBMTC will seek funding to address this issue by studying very young patients in the PBMTC database who underwent transplantation with and without TBI, comparing their neurocognitive and functional outcomes. This study also will address the neurocognitive implications of other transplantation preparative agents, such as busulfan, commonly used in this population and known to have long-term implications in pediatric transplantation survivors [26].

Another area of special concern in pediatrics is the treatment of opportunistic viral pathogens. The frequent use of cord blood (a relatively T cell–depleted product with slower immune recovery), transplantation in children with inherited immune deficiencies (often starting BMT with active viral infections), and transplantation in infants (immature immune systems) lead to unique infectious complications that warrant specific study. Whereas cytomegalovirus has been widely investigated, approaches to very young children with infections resulting from other pathogens, such as adenovirus, BK virus, and human herpesvirus-6 (HHV-6), require further study. Reports have demonstrated a mortality of 50% (27%-65%) from invasive adenovirus after allogeneic BMT [27,28]. More recent reports have shown improved outcomes using strategies that combine close monitoring for adenovirus with either preemptive or therapeutic cidofovir [29,30]. The use of cidofovir is limited by nephrotocixity, however, leaving patients with no other proven therapeutic options. New compounds, such as CMX001, a lipid-ester derivative of cidofovir, may be available for study in the near future [31]. Understanding the significance of BK and HHV-6 detection and infection, as well as the risks and benefits of therapy of these infections, also requires further study. The PBMTC, in partnership with industry and viral study groups, is committed to developing approaches to better understanding and treating these infections in the pediatric BMT setting.

In summary, PBMTC efforts in supportive care studies will focus on understanding the developmental impact of TBI and other types of intense preparative regimens in infants and younger children, and on understanding and treating unusual viral infections relatively common in pediatric BMT, including adenovirus, BK virus, and HHV-6.

## CONCLUSION

Advancement in several key areas of pediatric BMT will be strengthened by the newly formed partnership between the PBMTC and the CIBMTR/NMDP (RCI-BMT). This partnership will facilitate the accomplishment of important pediatric BMT priorities (Table 3). Close working relationships among the BMT CTN, the COG, and the PBMTC have been established and are vital in developing early-phase trials and then transitioning them to large phase II and III trials. Cooperation with disease-specific

groups, such as the Thalassemia Clinical Trials Network, the PIDTC and the LDN will further facilitate trial development. Finally, it it important to emphasize that the field will only move forward as governmental and non-governmental organizations recognize the unique aspects of pediatric BMT and fund trials that address the critical needs of this population.

## ACKNOWLEDGMENTS

*Financial disclosure*: This work is supported by a generous grant from the St Baldrick's Foundation. Further support is provided by Award U01HL069254 from the National Heart, Lung, and Blood Institute and the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the St Baldrick's Foundation, the National Heart, Lung, and Blood Institute, the National Cancer Institute, or the National Institutes of Health.

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## APPENDIX: PBMTC MEMBER INSTITUTIONS

### PBMTC Full Member Institutions

Alberta Children's Hospital, Calgary Alberta, Canada

All Children's Hospital, St Petersburg, Florida

The Floating Hospital for Children at Tufts Medical Center, Boston, Massachusetts

British Columbia Children's Hospital, Vancouver, British Columbia, Canada

CancerCare Manitoba, Winnipeg, Manitoba, Canada

Children's Healthcare of Atlanta at Egleston, Atlanta, Georgia

Seattle Children's / Fred Hutchinson Cancer Center, Seattle, Washington

Children's Hospital Oakland, Oakland, California

Children's Hospital of Los Angeles, Los Angeles, California

Children's Hospital of Michigan, Detroit, Michigan

Children's Hospital of Orange County, Orange, California

Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania

Children's Memorial Medical Center at Chicago, Chicago, Illinois

Children's National Medical Center, Washington, DC

Children's Hospital of New Orleans/LSU Medical Center, New Orleans, Louisiana

Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Cook Children's Hematology & Oncology Center, Fort Worth, Texas

Dana-Farber Cancer Institute, Boston, Massachusetts

Doernbecher Children's Hospital/Oregon Health & Sciences University, Portland, Oregon

Duke University Medical Center, Durham, North Carolina

Hackensack University Medical Center, Hackensack, New Jersey

CHU Sainte-Justine, Montreal, Quebec, Canada

Johns Hopkins Hospital, Baltimore, Maryland

Kosair Children's Hospital, Louisville, Kentucky

Levine Children's Hospital, Charlotte, North Carolina

Loma Linda University Medical Center, Redlands, California

Mayo Clinic, Rochester, Minnesota

M.D. Anderson Cancer Center, Houston, Texas

Medical University of South Carolina, Charleston, South Carolina

Methodist Children's Hospital of South Texas, San Antonio, Texas

Miami Children's Hospital, Miami, Florida

Midwest Children's Cancer Center / Medical College of Wisconsin, Milwaukee, Wisconsin

Mount Sinai School of Medicine, New York, New York

Nationwide Children's Hospital, Columbus, Ohio

Nemours Children's Clinic, Jacksonville, Florida

New York Medical College, Valhalla, New York

New York University Medical Center, New York, New York

Penn State University - Milton S. Hershey Medical Center, Hershey, Pennsylvania

Phoenix Children's Hospital, Phoenix, Arizona

Rady Children's Hospital San Diego, San Diego, California

Rainbow Babies & Children's Hospital / Case Western Reserve University, Cleveland, Ohio

Riley Hospital for Children, Indiana University, Indianapolis, Indiana

Roswell Park Cancer Institute, Buffalo, New York

Schneider Children's Hospital, New Hyde Park, New York

St Jude Children's Research Hospital, Memphis, Tennessee

Stanford University School of Medicine, Stanford, California

Texas Children's Cancer Center at Baylor College of Medicine, Houston, Texas

The Children's Hospital of Denver, Denver, Colorado

The Children's Mercy Hospital, Kansas City, Missouri

The Hospital for Sick Children, Toronto, Ontario, Canada

The Morgan Stanley Children's Hospital of New York – Presbyterian, New York, New York

The University of Chicago Comer Children's Hospital, Chicago, Illinois

UCLA Medical Center/ Mattel Children's Hospital, Los Angeles, California

University of Alabama at Birmingham, Birmingham, Alabama

University of Arizona Health Sciences Center, Tucson, Arizona

University of California Davis School of Medicine, Sacramento, California

University of California San Francisco School of Medicine, San Francisco, California University of Florida, Gainesville, Florida

University of Iowa Hospitals & Clinics, Iowa City, Iowa

University of Miami Jackson Memorial Hospital, Miami, Florida

University of Michigan Health System / C.S. Mott Children's Hospital, Ann Arbor, Michigan

University of Minnesota Cancer Center, Minneapolis, Minneapolis

University of Mississippi Medical Center, Jackson, Mississippi

University of Nebraska Medical Center, Omaha, Nebraska

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

University of Rochester Medical Center, Rochester, New York

University of Utah Medical Center / Primary Children's Medical Center, Salt Lake City, Utah

University of Wisconsin Children's Hospital, Madison, Wisconsin

University of Texas Southwestern Medical Center / Children's Medical Center, Dallas, Texas

Vanderbilt University Medical Center, Nashville, Tennessee

Virginia Common Wealth University Health System, Richmond, Virginia

Washington University-St. Louis Children's Hospital, St Louis, Missouri

Princess Margaret Hospital for Children, Perth, Western Australia, Australia

Royal Children's Hospital, Brisbane, Brisbane, Queensland, Australia

Starship Children's Hospital, Auckland, New Zealand

The Children's Hospital at Westmead, Westmead, New South Wales, Australia

### PBMTC Associate Member Institutions

Cancer Institute of New Jersey, New Brunswick, New Jersey

Cardinal Glennon Children's Medical Center-Saint Louis University, St Louis, Missouri

Children's Hospital of Central California, Madera, California

Children's Hospital Medical Center of Akron, Akron, Ohio

Children's Hospital of Montefiore, Bronx, New York

Children's Hospitals and Clinics of Minnesota, Minneapolis, Minnesota

DeVos Children's Hospital, Grand Rapids, Michigan

Florida Hospital Cancer Institute, Orlando, Florida

Maine Children's Cancer Program, Scarborough, Maine

McGill University Health Center - Montreal Children's Hospital, Montreal, Quebec, Canada

Medical College of Georgia, Augusta, Georgia

National Cancer Institute, Bethesda, Maryland

St Christopher's Hospital for Children, Philadelphia, Pennsylvania

Stollery Children's Hospital, Edmonton, Alberta, Canada

Tulane University/Tulane University Hospital & Clinic, New Orleans, Louisiana

University of Hawaii/Kapiolani Med Center for Women & Children, Honolulu, Hawaii

University of Arkansas for Medical Sciences, Little Rock, Arkansas

University of Kentucky Markey Cancer Center / A.B Chandler Medical Center, Lexington, Kentucky

Yale University School of Medicine, New Haven, Connecticut

Colombian Childhood Cancer Parents Organization, Bogota, DC, Colombia

Hospital de Clinicas de Porto Alegre, Porto Alegre, RS, Brazil

Instituto de Oncologia Pediatrica, Sao Paulo, Brazil

Ramathibodi Hospital, Bangkok, Thailand

Royal Children's Hospital, University of Melbourne, Parkville, Victoria, Australia

Sydney Children's Hospital, Sydney, New South Wales, Australia

University Hospital Brno, Brno, Czech Republic

Women & Children's Hospital, Adelaide, North Adelaide, South Australia, Australia