

# Blood and Marrow Transplant Clinical Trials Network State of the Science Symposium 2007

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## ABSTRACT

Outcomes of hematopoietic cell transplantation are steadily improving. New techniques have reduced transplant toxicities, and there are new sources of hematopoietic stem cells from unrelated donors. In June 2007 the Blood and Marrow Transplant Clinical Trials Network convened a State of the Science Symposium of more than 200 participants in Ann Arbor to identify the most compelling clinical research opportunities in the field. This report summarizes the symposium's discussions and identifies eleven high priority clinical trials that the network plans to pursue over the course of the next several years.

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## KEY WORDS

Hematopoietic cell transplantation • Clinical Trials Network • Clinical trials • Graft versus host disease • Acute myeloid leukemia • Acute lymphocytic leukemia • Chronic lymphocytic leukemia • T cell lymphoma • Hemophagocytic lymphohistiocytosis • Crohn's disease • Cell therapy • Biomarkers • Quality of life

## INTRODUCTION

Over the past 20 years, the number of hematopoietic stem cell transplants (HSCTs) has increased at a rate of 2000 transplants per year so that today approximately 50,000 transplants are performed annually worldwide. Despite the increasing use of this complex and intensive therapy, very few patients enter clinical trials. The reasons are multiple, and include all the usual barriers to the conduct of clinical research in sick patient populations. In addition, obstacles to clinical trials of HSCT are amplified by the limited number of patients per center and heterogeneity in risk factors, such as the type and stage of primary diagnosis, the age of the donor and recipient, the type and source of donor stem cells, and transplant technique, among others.

In 2001, the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI) chartered the Blood and Marrow Transplantation Clinical Trials Network (BMT CTN) to address these problems and conduct HSCT clinical trials that would advance the standard of care for transplant patients. In preparation for this charter, a State of the Science Symposium (SOSS) was convened, which defined 6 key areas that would help frame the scientific agenda of the BMT CTN: optimal graft source and composition, regimen related toxicity, graft-versus-host disease (GVHD), infection and immune reconstitution, quality of life/late effects, and relapse of malignancy following HSCT. The BMT CTN has now been operational for nearly 6 years, with a total accrual of almost 2000 patients into trials. To frame the scientific agenda

for the next 5 years, the network planned a second SOSS organized in 12 committees. The initial area of relapse of malignancy was expanded to 3 committees, including leukemia, lymphoma, and multiple myeloma, to better address the disease-specific issues inherent in these diagnoses. Committees in pediatrics, nonmalignant diseases, cell and gene therapy, and strategies for successful trial design and implementation were added.

To gain the widest perspectives possible, individual members of the BMT CTN steering committee each participated in only 1 SOSS committee, and all committees were composed primarily of individuals outside the network leadership. In addition, members of the NCI cooperative groups were included in all the malignancy committees (leukemia, lymphoma, multiple myeloma). Intensive committee work began in September 2006, and after multiple meetings, draft reports from all 12 committees were reviewed before the symposium, by a panel of international experts who led the question periods during the SOSS in Ann Arbor. Where sufficient preliminary data existed and the committee members reached consensus, they proposed 1 or more trials, presented here with a background, hypothesis, design, and feasibility considerations. In the absence of sufficient data or consensus, a more general strategy was proposed. This article summarizes the discussion of all the committees, and concludes with a list of the trials that were endorsed most enthusiastically by the Symposium leadership.

#### CURRENT BMT CTN TRIALS

- 0101 Phase III randomized comparison of fluconazole versus voriconazole for the prevention of invasive fungal infections after allogeneic HSCT.
- 0102 Phase III biologic assignment comparison of double autologous HSCT versus tandem autologous/allogeneic HSCT for patients with multiple myeloma.
- 0201 Phase III randomized comparison of granulocyte-colony stimulating factors (G-CSF) mobilized peripheral blood stem cells (PBSC) versus bone marrow from HLA-identical unrelated donors.
- 0301 Phase II trial of fludarabine-based conditioning for allogeneic HSCT from HLA-identical unrelated donors in severe aplastic anemia (AA).
- 0302 Phase II randomized comparison of etanercept, mycophenolate mofetil (MMF), denileukin diftitox, and pentostatin, in combination with corticosteroids as initial systemic treatment of acute GVHD.
- 0303 Phase II trial of HLA identical, CD34+ enriched, T cell-depleted, peripheral blood HSCT for patients with acute myelogenous leukemia (AML) in first or second remission.
- 0401 Phase III randomized comparison of rituxan/beam versus bexxar/beam with autologous HSCT for diffuse large B cell lymphoma.
- 0402 A Phase III randomized comparison of tacrolimus/sirolimus versus tacrolimus/methotrexate (MTX) as GVHD prophylaxis after HLA-identical related donor HSCT.
- 0403 Phase III randomized comparison of etanercept versus placebo for treatment of idiopathic pneumonia syndrome.
- 0501 Phase III randomized comparison of single versus double umbilical cord blood (UCB) transplantation in pediatric patients with high-risk leukemia and myelodysplasia.
- 0502 Phase II study of nonmyeloablative allogeneic HSCT for older patients with AML in complete remission (CR).
- 0601 Phase II study of nonmyeloablative unrelated donor HSCT for children with severe sickle cell disease.

#### COMMITTEE I. OPTIMAL DONOR AND GRAFT SOURCE

##### Current State of the Science

HSCTs from other than HLA-identical siblings are associated with greater risks of graft rejection, GVHD, infection, and death. Mobilized blood is now the most frequent source of stem cells from volunteers, and an ongoing BMT CTN Phase III trial is comparing marrow and mobilized blood cells from adult volunteers.

Phase II BMT CTN trials of reduced intensity (RIC) regimens in older patients testing double unit cord blood grafts, and T-replete haplotype-mismatched related transplant with postgrafting cyclophosphamide are in development. We believe the following 2 trials represent important research opportunities.

##### Trial I. Unrelated Donor Transplantation versus Chemotherapy for High-Risk AML

*Background and Hypothesis.* AML is the primary indication for unrelated transplantation, usually after chemotherapy failure. Randomized trials and 2 meta-analyses have shown that HLA-identical sibling grafts improve survival compared to chemotherapy [1,2]. Survival of AML patients with high-risk cytogenetics transplanted in first remission is similar (30%), whether the donors are HLA-identical siblings or unrelated volunteers [3]. We will test the hypothesis that unrelated donor transplantation soon after induction

chemotherapy improves survival of patients with AML compared to treatment with best chemotherapy.

*Trial Design and Feasibility.* We propose a Phase III trial comparing unrelated donor transplantation to chemotherapy for AML patients with high-risk cytogenetics, aged 18-60 years, in collaboration with U.S. and European cooperative groups. At diagnosis, patients will have cytogenetics and HLA typing performed, siblings will be HLA typed, and unrelated donor searches of patients with AML coordinated as needed. The treatment arm will be allocated according to whether a HLA-matched sibling or volunteer donor is identified. In 225 patients having an unrelated donor and 122 have no donor, there will be an 80% power to detect a 15% difference in 3-year survival between the treatments, anticipating 30% versus 15% patients alive. A total of 2000 AML patients is required: 30% (600) will have high-risk cytogenetics, 80% (480) will survive 6 months, and 75% (360) will have no HLA-identical sibling. Challenges are the cooperation between groups to enroll 600 AML patients with high-risk cytogenetics over a reasonable time, and the coordination of timely HLA typing and a donor search.

### **Trial 2. Cord Blood versus Adult Stem Cell Sources from Unrelated Donor**

*Background and Hypothesis.* Both cell dose and HLA mismatching are barriers to cord blood engraftment. Preliminary data indicate that transplantation of 2 partially HLA-matched cords overcome graft resistance in adults and reach similar survival as adult marrow grafts [4,5]. We will test the hypothesis that if the cell dose barrier to engraftment can be overcome, cord blood will be safer than adult stem cell sources.

*Trial Design and Feasibility.* We propose a randomized Phase III study of 8/8 HLA-A, -B, -C, -DRB1 matched volunteer and a 6 of 6 or 5 of 6 cord blood graft consisting of 1 or 2 units (depending on the available dose) or a 7 of 8 volunteer and a double unit 4 of 6 cord blood graft. The primary endpoint is 3-year survival. A sample size of 732 patients will have an 80% power to detect a difference of 10% between the 2 graft sources. Cord blood use for adults will likely increase and by the time an ongoing Phase II Center for International Blood and Marrow Transplant Research (CIBMTR) trial is completed, a sufficient number of adult patients will be referred for cord blood transplantation to make a Phase III trial feasible.

### **Discussion Summary**

There was high enthusiasm at the meeting for the trial of Unrelated Donor Transplant versus Nontransplant Chemotherapy for High Risk AML that was presented by both committees 1 and 7. The Phase III

trial of cord blood versus adult stem cells was deferred contingent upon successful completion of the CIBMTR double unit cord blood trial.

## **COMMITTEE 2. REGIMEN RELATED TOXICITY**

### **Current State of the Science**

HSCT is associated with significant nonrelapse mortality (NRM) mainly from GVHD and regimen-related toxicities (RRT). Mucositis, veno-occlusive disease (VOD) of the liver (also known as sinusoidal obstruction syndrome) and pulmonary toxicity (PT) occur in 5%-10% of HSCT patients following myeloablative conditioning and account for approximately 30% of deaths. The ability to predict RRT risk is poor, and better prediction should improve outcome [6-8]. Efforts to reduce RRT have focused on reducing regimen intensity rather than direct prevention or early treatments, although a Phase III BMT CTN trial using etanercept to treat PT is about to open [9].

### **Trial 1. Genetic Predictors for Risk of Regimen-Related Organ Toxicities after HSCT**

*Background and Hypothesis.* Variability in the expression of genes associated with mechanistic pathways of RRT has not been extensively studied. Prior studies have validated the concept of mechanistically based genetic risk prediction on only a small set of specific genes and polymorphisms [6,10,11]. In addition, because it is likely that cooperative genes influence outcome, single nucleotide polymorphisms (SNPs) of a single gene fail to take into account the multigenetic nature and associations of complex traits. Genome-wide genotyping using new Bayesian network statistical approaches are now available, and can be used on large datasets to define mechanistic associations [12,13]. We will test the hypothesis that risks for RRT are largely determined by genetic factors, and that these risks can be predicted by individual genotyping using SNPs analysis.

*Trial Design and Feasibility.* Patients enrolled on BMT CTN 0101 have all undergone myeloablative allogeneic HSCT in the last 3 years with comprehensive clinical data and banked samples of DNA available. Genome-wide genotyping of a subset of these samples will be conducted. A prognostic model for toxicities will be generated and validated in a prospective population. Information gained from patterns of SNP associations should lead to potential targets for therapeutic intervention. Genotyping of 200 samples banked from BMT CTN 0101 patients with RRT will be compared to 100 samples from controls without organ toxicity. The GeneChip® Human Mapping 500K Array Set will be used to develop a prognostic model using Bayesware Discoverer software, and will

be validated with a second sample of 200 patients treated in subsequent BMT CTN trials.

### **Trial 2. Pulmonary Function Monitoring and Early Evaluation of Pulmonary Toxicity after Allogeneic HSCT**

*Background and Hypothesis.* Pulmonary toxins are commonly used in HSCT regimens (eg, busulfan, carmustine, and radiation) and pulmonary complications remain a cause of HSCT RRT. Posttransplant pulmonary function test (PFT) monitoring is not standardized, and detection of pulmonary abnormalities often occurs after toxicity is irreversible. Earlier testing may lead to earlier and more targeted therapy. We will test the hypothesis that scheduled PFT with early CT scanning and bronchoscopy will result in earlier detection of pulmonary toxicity and lead to therapies.

*Trial Design and Feasibility.* Patients undergoing myeloablative or reduced-intensity allogeneic HSCT will undergo PFTs (spirometry and diffusing capacity) pretransplant and monthly for 6 months and then every 2 months until 1 year. A significant decline in FEV1 or diffusing capacity or an increase in residual volume will initiate radiology (chest X-ray and chest CT), bronchoscopy, with bronchoalveolar lavage, and biopsy with concurrent blood samples for cytokine analysis. The incidence of pulmonary toxicities is expected to be 5%-10%; 300 patients would need to be enrolled to obtain 20 affected patients. Estimated accrual of over 600 patients in BMT CTN studies within the next 4 years suggest this is feasible.

### **Discussion Summary**

Discussion concerning the genotyping proposal to understand the intra-patient variability of RRT was very positive. A Biomarkers Committee will be formed to further consider the best use of DNA and cellular and serum samples collected during BMT CTN trials to answer this and other correlative questions. The discussion of the pulmonary toxicity monitoring project concluded that a final trial design should await availability of results of ongoing pilot studies from University of Washington, Seattle, and the University of Michigan.

## **COMMITTEE 3. GVHD**

### **Current State of the Science**

The ability to make HSCT more effective will require improved control of both GVHD and graft-versus-leukemia effects (GVL). The critical criteria for successful HSCT are the reduction of the morbidity of GVHD while maintaining an effective GVL response and allowing effective immune recovery. Critical to the mission of the BMT CTN are studies

of both prevention and therapy of acute and chronic GVHD (aGVHD, cGVHD). GVHD prophylaxis typically depends on a calcineurin inhibitor (CNI) based on studies from the 1980s [14,15]. Cellular engineering approaches focusing on depletion of T cells from the stem cell product have not been consistently successful and have not improved survival. Two active prophylaxis trials, BMT CTN 0303 and BMT CTN 0402, address important issues in matched related donors. Primary therapy for GVHD is currently under investigation in BMT CTN 0302. Trials are now in development to explore alternative sources of hematopoietic stem cells, including haploidentical donors and 2 UCB units. Trials will be needed to progress rationally from the current BMT CTN portfolio to the next series of Phase III trials. Two approaches should be helpful in moving forward: (1) approaches to improve our understanding and treatment of cGVHD, and (2) Phase II trials of GVHD prophylaxis.

### **Trial 1. A Randomized Phase II Trial for High-Risk cGVHD**

*Background and Hypothesis.* Evolving understanding of immunologic control mechanisms suggests that manipulation of cellular populations other than conventional T cells, either in vivo or ex vivo, may be beneficial. CNI inhibit both regulatory T cells (Treg) and conventional T cells and may interfere with thymic function [16,17]. It is possible that observed rates of cGVHD relate to the inability of CNI to induce long-term tolerance [18-20]. Augmentation of natural or inducible Treg number or function may mitigate GVHD and facilitate immune competence while maintaining GVL [21]. Several approaches to augment Treg numbers or activity are feasible. Sirolimus based, CNI-free regimens (eg, sirolimus/MMF) may foster Treg whereas inhibiting effector T cells. In mouse models GVHD is prevented, whereas GVL is maintained [21]. Extracorporeal photopheresis (ECP) also may enhance Treg numbers while modulating APC function. ECP could be used as prescriptive therapy for both aGVHD and cGVHD [22-24], although clinical data for this approach is minimal. We will test the hypothesis that treatment without calcineurin inhibitors will improve outcomes for high risk cGVHD patients.

*Trial Design and Feasibility.* Criteria to define high-risk cGVHD are under discussion. A 3-arm trial would be most straight forward, but practices regarding ECP vary widely between centers, and this lack of equipoise may favor 2 parallel Phase II studies with a common comparator arm, with all patients receiving sirolimus. A major limitation in the design of cGVHD trials is our primitive understanding of the pathophysiology of cGVHD. In these trials, prospective clinical data matched to biomarker studies should be col-

lected. Prospective clinical trials must include detailed multimodality assessment of symptoms, functions, and clinical status to determine which manifestations are best amenable to reversal and best correlate with reduction in NRM. Comprehensive biomarker analysis in cGVHD should guide further exploratory and therapeutic studies [25]. We recommend the initiation of detailed, prospective assessments of biomarkers of cGVHD risk and relevant modulating factors. Studies should target the development of cGVHD, resistance to therapy, and relapse.

**Strategy 2.** Animal studies show that depletion of host antigen presenting cells (APCs) pre-HSCT or donor plus host APCs after HSCT may prevent GVHD [26,27]. Some single-center Phase II studies are currently exploring this approach to GVHD prophylaxis.

**Strategy 3.** Limited data suggest that enhancement of natural killer T cell (NKT) populations may limit GVHD, whereas sparing GVL [28]. Either endogenous NKT cell function could be enhanced or ex vivo selection and infusion of NK cells could be pursued. Alternatively, KIR selection strategies permissive of NK alloreactivity may limit GVHD.

#### Discussion Summary

Considerable interest focused on the need for more preclinical work before we embark on trials designed to enhance Treg activity or modulation of APC numbers and function. In addition, the discussion identified the need for better understanding of the presentation of early-stage GVHD and the response of early-stage GVHD to therapy. Future trials will address these considerations by building on the current BMT CTN portfolio.

### COMMITTEE 4. INFECTION AND IMMUNE RECONSTITUTION

#### Current State of the Science

Delays in immune reconstitution or suboptimal recovery of immune function place the HSCT patient at prolonged risk for serious infection. The goal of any strategy to boost immune reconstitution is to prevent serious infection or reduce the interval of risk. The BMT CTN conducted a Phase III trial of antifungal prophylaxis in 600 allogeneic transplant patients comparing voriconazole to fluconazole with intensive galactomannan monitoring to determine the 6-month survival free of invasive fungal infection as the primary endpoint. Analysis of results will be known in late 2007. The BMT CTN is also conducting a prospective immune assessment using a limited number of immune assays as part of a Phase III trial in matched unrelated donor transplant recipients comparing pe-

ripheral blood to bone marrow as stem cell graft source. This trial has reached the halfway point in accrual; results will not be known for several years.

**Strategy 1. Detailed, Multicenter Longitudinal Studies of Functional Immune Reconstitution.** A number of single-center studies of global and pathogen-specific immune responses over time have been performed. Knowledge about the pace and extent of cellular and humoral immune reconstitution and information about factors that influence the pace of recovery is incomplete. Moreover, changes in transplant practices have occurred and considerable gaps in knowledge exist regarding the influences of several key variables, including the donor immune status prior to donation, the use of particular agents in the preparative regimen, age-related thymic involution, graft type, immunosuppressive regimens, and the type of donor. Different assays at different centers and different mixtures of types of patients make generalizations from studies at single centers difficult. Functional assays that allow more in-depth evaluation of immune reconstitution is complicated by the lack of understanding of standardized antigen preparations, particularly for pathogens with large antigen profiles, such as fungi. Finally, there is a lack of knowledge as to which assay (if any) predicts patients at greater risk for delayed or incomplete immune recovery.

**Strategy 2. Boost Global Immune Reconstitution.** Several molecules to enhance global immune reconstitution have been tested in preclinical models, and Phase I and II clinical trials are now underway in various stages. These include keratinocyte growth factor (KGF) [29-31], luteinizing hormone-releasing hormone (LHRH) agonist [32], and interleukin (IL)-7 [33,34]. Another molecule, IL-15, holds promise in preclinical models [35,36]. Findings from these trials will become known within the next 2 to 3 years, at which time we envision a Phase III trial of the most promising immunomodulatory molecule. Another approach to improve global immune reconstitution is to avoid immunosuppression posttransplant. Addbacks of certain cellular subsets selected to speed recovery may be part of such a strategy, but would be intimately involved in considerations of GVHD prophylaxis.

**Strategy 3. Enhance Pathogen-Specific Immunity.** Several clinical trials are underway to test vaccine strategies for pertinent pathogens that are important for HSCT. These include the protein-conjugate pneumococcal vaccine [37-39], inactivated VZV vaccine [37-40], and inactivated CMV vaccine [41]. These are being tested in adults with ablative conditioning regimens in allogeneic transplants using both sibling and unrelated donors. Several anti-CMV adoptive immunotherapy studies are also now underway. A Phase II study showed that the strategy of

prophylactic cytomegalovirus (CMV)-specific T cell therapy resulted in a similar rate of CMV disease but decreased the need for antiviral drugs and was associated with less neutropenia. Questions remain regarding the optimal composition and antigen specificity of the cellular product, standardization of immune function assays, clinical endpoints, use of antivirals, and logistical issues as to the manufacturing of the cells for large multicenter studies under GMP conditions.

### Discussion Summary

Numerous comments were made of the need for reaching consensus on a standardized set of immune assays and timing of assessment before a therapeutic trial could be launched. The importance of defining safety of candidate interventions in pilot studies was emphasized.

## COMMITTEE 5. LATE EFFECTS/QUALITY OF LIFE

### Current State of the Science

The BMT CTN has not conducted specific trials in late effects or quality of life (QOL). However, several trials incorporate QOL measures as secondary endpoints. Please note that treatment of cGVHD is addressed by the GVHD committee.

### Trial 1. Educational Intervention to Improve Health Screening

*Background and Hypothesis.* Limited data in HSCT survivors suggest they are no more likely to undergo preventive health procedures and engage in healthy behaviors than the general population despite a high incidence of late adverse treatment effects, frequent contact with the medical system, and elevated rates of morbidity and mortality. We will test the hypothesis that an educational intervention targeted at patients and/or physicians including structured reminders will improve compliance with recommendations for cancer screening, appropriate organ function testing, and screening for psychosocial distress when compared to standard care.

*Trial Design and Feasibility.* We propose a Phase III randomized trial to compare usual care to an intervention that heightens attention to potential medical, functional, and psychosocial complications after HSCT [42,43]. To improve standardization, accessibility, and generalizability, the intervention will be comprised of mailed information and web-based materials and/or phone calls delivered after HSCT. The study would use an intermediate endpoint, such as patient self-reported screening rates, health behaviors, and detection and treatment of late effects, as surrogates for improving the health of survivors. Generation of pilot and feasibility data for the intervention would be required.

### Trial 2. Stress Management to Improve Physical and Emotional Functioning

*Background and Hypothesis.* Many studies have documented deficits in QOL after HSCT but few have focused on testing interventions to improve QOL and functioning. Data from single centers suggest that exercise and stress management improves QOL and functional status in HSCT recipients [44-50]. We will test the hypothesis that participation in an exercise and stress management program reduces fatigue and stress and improves QOL in HSCT recipients.

*Trial Design and Feasibility.* We propose a Phase III randomized trial to compare usual care to a stress management intervention based upon exercise and relaxation/imagery techniques. The primary endpoints will be QOL and functional status. The advantages of such a study are: (1) high patient interest in an intervention aimed at improving QOL, (2) lack of competing studies, (3) abundant preliminary data to support conduct of a multicenter Phase III trial. Challenges include: (1) standardization of the intervention, (2) infrastructure at each center to deliver the intervention, (3) logistic difficulties associated with collection of patient-reported outcomes. Use of a self-administered intervention would mitigate the first 2 concerns.

### Trial 3: Standardized Collection of Patient-Reported Outcomes

*Background and Hypothesis.* Several ongoing BMT CTN studies collect patient-reported outcomes including QOL and functional status. Lack of agreement about the specific instruments, assessment points, data collection methods, and analysis plans limit QOL comparisons across trials. We will test the hypothesis that incorporation of a manageable set of QOL/symptom instruments across randomized trials will allow inter and intratrial comparisons.

*Trial Design and Feasibility.* Instruments will capture sociodemographic and work/school items for both pediatric and adult populations. Collection of QOL information prior to transplantation and at 1 and 3 years after HSCT would mirror the recommendations of the Stem Cell Transplant Outcomes Database (SCTOD). The core set of measurements should not require more than 10-15 minutes to complete. Some trials will require additional instruments and/or time points to address specific scientific questions. An on-line version of the core assessment would improve data quality and reduce long-term costs when used by patients with Web access. Housing QOL data in a reference database within the BMT CTN will facilitate cross/trial analysis. The major barrier to implementation will be adequate infrastructure at individual sites to collect high quality QOL data.

## Discussion Summary

Audience comments focused on the feasibility of the proposed interventions, data collection, the validity of the instruments and expected effect sizes, a potential placebo effect, anticipated difficulties with missing data, and whether additional study is necessary to know “best practices.” There was also discussion about whether children could be included in the proposed studies.

## COMMITTEE 6. PEDIATRICS

### Current State of the Science

HSCTs in children and adolescents account for 20%-25% of all HSCTs performed in North America. Currently, more than 40% of unrelated donor transplants in children utilize UCB as the stem cell source (M. Eapen, personal communication). The BMT CTN, together with Children’s Oncology Group (COG), is currently conducting a randomized Phase III trial testing whether the double cord blood transplants improve survival and engraftment and decreases the rate of leukemic relapse without increasing the rate of GVHD compared to single cord blood transplants. BMT CTN 0601 is a Phase II trial of nonmyeloablative unrelated donor HSCT for children with severe sickle cell disease. Two additional areas of HSCT trials applicable to children could be developed in the next additional 5 years.

### Trial 1. Reduced Intensity Conditioning (RIC) for Hemophagocytic Lymphohistiocytosis (HLH)

*Background and Hypothesis.* Hemophagocytic disorders are comprised primarily of HLH, but also include X-linked lymphoproliferative syndrome (XLP), Chediak-Higashi syndrome, and Griscelli syndrome. These nonmalignant syndromes are often fatal, and are characterized by hyperproduction of inflammatory cytokines such as tumor necrosis factor alpha (TNF). The diagnosis of HLH can be established by genetic and functional testing. Allogeneic HSCT is the only curative option but early transplant-related mortality (TRM) of 35% is a major barrier to success [51]. We will test the hypothesis that RIC will result in improved survival by decreased treatment-related mortality without loss of efficacy for patients with HLH.

*Trial Design and Feasibility.* We propose a definitive Phase II trial with a primary endpoint of day 100 mortality. Pilot data [52,53] suggest that an RIC regimen is safe and effective in children with nonmalignant disorders, including HLH. Inhibition of TNF during transplant may be desirable both because TNF is implicated in transplant-related complications and is a specific mediator in HLH. In 2006, 26 transplants for HLH were registered at the CIBMTR. A single reference laboratory for HLH in North America pro-

vides an opportunity to characterize the disease at diagnosis. Accrual of 40-50 patients is feasible within 4 years.

### Trial 2. Post HSCT Immunomodulation for Pediatric Acute Lymphoblastic Leukemia

*Background and Hypothesis.* Leukemia relapse accounts for the majority of failures after transplant for acute lymphoblastic leukemia (ALL) [54]. One possible strategy is control of post-HSCT minimal residual disease (MRD). The mTOR inhibitor sirolimus to control MRD [55,56] and MTX is highly synergistic with sirolimus in preclinical models of ALL. Alternative strategies would be the use of TLR7 and TLR9 agonists, which alter the immunogenicity of ALL blasts as well as induce an immunologically mediated antileukemia response [57,58]. A TLR7 agonist (imi-quimod) is currently under investigation for refractory leukemia patients [59]. We will test the hypothesis that one of these agents will decrease leukemia relapse when used as maintenance therapy after HSCT.

*Trial Design and Feasibility.* Because the majority of relapses occur in the first post-HSCT year, the primary endpoint will be 1-year event-free survival. Maintenance therapy post-HSCT with a toll-like receptor agonist will begin within several weeks of the transplant and continue for the 1 year. One or more of these agents mentioned above should be available for Phase II trials within the next 4 years. Collaboration between the COG and the BMT CTN will ensure adequate accrual.

## Discussion Summary

There was a high level of enthusiasm by all HSCT physicians as well as support by the pediatric HSCT community for the HLH proposal. Further preliminary studies were thought to be required to develop immune modulation after HSCT. Pediatricians also strongly supported the prioritization of HSCT studies in lysosomal disorders, severe combined immune deficiencies, and hemaglobinopathies, as funding becomes available.

## COMMITTEE 7. LEUKEMIA

### Current State of the Science

Leukemia is the most common indication for HSCT. As HSCT outcomes improve, there is clinical use of HSCT as early therapy for various leukemias. But new agents also have increased efficacy, and there are almost no comparisons of these therapeutic approaches. The committee selected from the following trials a large number of potentially important questions based on their broad relevance, the existence of sufficient preliminary data to warrant rapid activation of network-wide studies, and the likelihood of successful completion. Trials are organized by type of leukemia.

**ALL****Trial 1. A Prospective Trial of Allogeneic HSCT and Modern Chemotherapy for Adult Ph+ ALL in First CR**

*Background and Hypothesis.* Prior to the availability of imatinib and other BCR-ABL tyrosine kinase inhibitors, the outlook for patients with Ph+ ALL treated with conventional chemotherapy was extremely poor, and accordingly, allogeneic transplantation was the treatment of choice. Recently, several groups using imatinib in combination with conventional chemotherapy have reported outcomes in Ph+ ALL that rival those obtained with allogeneic transplantation [60-62]. Preliminary data suggest that the more potent tyrosine kinase inhibitor, dasatinib, can be combined with intensive chemotherapy safely. We will test the hypothesis that modern chemotherapy incorporating a tyrosine kinase inhibitor will yield disease-free survival (DFS) similar to that achieved with allogeneic HSCT.

*Trial Design and Feasibility.* We propose a Phase III, "biologic assignment" design. Patients will be entered at diagnosis and receive an allogeneic transplant in first CR if an appropriate donor is available, or be treated with HyperCVAD + dasatinib. Because patient evaluation will begin at diagnosis, this trial would be conducted in collaboration with cooperative groups. If the outcome of such a combination is equivalent to that achieved with allogeneic HSCT, then allogeneic HSCT could be reserved for patients at high risk of relapse or who have molecular evidence of MRD.

**Trial 2. A Prospective Trial of Reduced Intensity Allogeneic HSCT for Patients with Ph- ALL in First CR Aged 35-60 years**

*Background and Hypothesis.* The recent MRC UKALL XII/ECOG E2993 trial demonstrated that for patients with Ph- ALL, HLA-matched sibling allogeneic transplantation results in a statistically significant improvement in survival, when compared to conventional chemotherapy [63]. This advantage was reduced in patients above age 35 because of an increase in TRM. We will test the hypothesis that the advantages of allogeneic HSCT in Ph- ALL in first remission in patients over age 35 can be improved using a less intensive preparative regimen.

*Trial Design and Feasibility.* We propose a Phase II trial in which patients with Ph- ALL, aged 35-60 years with matched siblings or appropriately matched unrelated donors will be treated with a transplant regimen of melphalan plus fludarabine. This question can be approached in an upcoming intergroup ALL study.

**AML****Trial 1. A Prospective Trial of Allogeneic Transplantation versus Chemotherapy for Adults with AML in First CR Aged > 60 years**

*Background and Hypothesis.* The outcome for patients with AML over age 60 treated with conventional chemotherapy is generally poor, with a median DFS of 7-9 months and fewer than 15% alive disease-free at 3 years [64]. Several groups have recently reported encouraging results using RIC regimens for this group of patients, including 3-year DFS rates of 44% for recipients of matched related transplants and 63% after matched unrelated transplantation [65]. There is a need to confirm these results in a prospective trial in which patients achieving CR are treated with transplantation if a suitable donor is available and those without donors treated with chemotherapy. We will test the hypothesis that reduced intensity allogeneic transplantation from a matched sibling or unrelated donor will provide longer survival compared with chemotherapy.

*Trial Design and Feasibility.* If the advantage with transplantation persists, this would change the standard of therapy for this group of individuals. A large trial of this type could only be performed in close collaboration with NCI cooperative groups. Representatives from all the groups have participated in this committee and are enthusiastic about the proposal.

**Trial 2. A Prospective Randomized Trial of RIC versus Conventional Intensity Conditioning in Patients with AML Aged 35-60 years**

*Background and Hypothesis.* RIC regimens in older patients with AML in first remission are associated with relapse rates not too dissimilar from those seen with more intensive regimens in younger patients. Thus, the conduct of a prospective randomized comparison of a conventional intensive preparative regimen with an RIC regimen in middle-aged (35-60) patients with AML is warranted. We will test the hypothesis that any increase in relapse rates caused by a reduction in the intensity of conditioning in patients aged 35-60 years will be balanced by a reduction in TRM, leading to a safer and ultimately equally effective regimen.

*Trial Design and Feasibility.* Should equivalence be seen in the two approaches, this would both provide a safer and equally effective approach for patients, and would also provide a platform onto which leukemia-specific therapies might be more easily added.

**Trial 3. Unrelated Donor Transplantation versus Chemotherapy for High-Risk AML**

*Background and Hypothesis.* A recent meta-analysis of all studies published since 1995 that compare chemotherapy with allogeneic transplantation from

matched siblings for adults aged 17-60 years reported a statistically significant survival advantage with allogeneic transplantation [1]. This advantage was particularly evident for patients with high-risk disease, as defined by cytogenetics. Use of alternative donors for this group of patients is unsettled, but single prospective trial suggests an advantage for unrelated donor transplantation [66]. We propose a prospective trial comparing the results of unrelated allogeneic transplantation with conventional chemotherapy in younger patients (aged < 60 years) with high-risk AML in first remission.

*Trial Design and Feasibility.* The details of this trial are discussed in more detail in the report of Committee 1.

### CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

#### **Trial 1. A Phase II Trial of Reduced Intensity Allogeneic Transplantation for Patients with very High-Risk CLL**

*Background and Hypothesis.* Approximately 25% of patients with CLL will have chromosomal abnormalities involving 17p13.3 and 11q22-23. These patients tend to have a particularly aggressive form of CLL, with a higher likelihood of transformation to an aggressive lymphoma and a shorter overall survival (OS) [67]. Preliminary results with reduced intensity allogeneic transplantation in patients with fludarabine-resistant CLL have yielded encouraging results [68]. Thus, a question of considerable interest would be the utility of reduced intensity allogeneic transplantation applied early in the course of patients with cytogenetically defined high-risk disease. We will test the hypothesis that reduced intensity allogeneic HSCT will improve survival compared to historical controls in patients with very high-risk CLL.

*Trial Design and Feasibility.* Given the limited preliminary data and the great variability of CLL patients, we acknowledge that a randomized trial is premature and would be difficult to perform. However, a Phase II trial of this approach would be informative and of high interest.

### CHRONIC MYELOGENOUS LEUKEMIA (CML)

The use of HSCT in the treatment of CML is now largely limited to patients who have failed treatment with tyrosine kinase inhibitors. Although a large number of questions exist about the appropriate use of transplantation in CML, including, for example, the importance of molecular monitoring to allow early transplant in patients developing tyrosine kinase resistance, the committee was unable to identify a clinical trial in CML with a high likelihood of successful

completion because of small numbers of patients and the rapid development of new drugs.

### MYELODYSPLASIA (MDS)

Patients with MDS, who are transplanted with earlier stage disease (as determined, for example, by International Prognostic Scoring System [IPSS]) tend to have a superior outcome [69]. However, it is unknown whether attempts to improve the IPSS score pretransplant result in an overall clinical benefit. The committee recognized that a question of general interest is the utility of DNA methyl-transferase inhibitor therapy prior to proceeding to an allogeneic transplant (for patients with intermediate-2/high-risk MDS) [69a]. However, concerns about the likelihood of successfully completing such a study prevented its inclusion on our high priority list.

### Discussion Summary

High enthusiasm was expressed for all trials. There was some concern expressed regarding the feasibility of the AML trials. The audience appreciated the thoughtful deliberations of the committee and was especially enthusiastic about potential collaborations between the BMT CTN and the NCI cooperative groups to ask these important questions regarding the role of HSCT as primary therapy for several leukemias.

### COMMITTEE 8. LYMPHOMA

#### **Current State of the Science**

HSCT is a proved curative treatment modality for many patients with non-Hodgkin lymphoma (NHL) and Hodgkin disease, but relapse after HSCT remains the leading cause of treatment failure. The BMT CTN is exploring strategies to reduce the risk of lymphoma relapse, including incorporation of novel treatments such as radioimmunoconjugates to augment the conditioning regimen. Identification of important biologic characteristics to guide these therapies or provide earlier recognition of high-risk patients is central to these goals.

**Strategy 1.** Allogeneic nonmyeloablative conditioning regimen is a recent advance in the field of HSCT that has broadened its applicability. A growing number of published reports have demonstrated the efficacy of nonmyeloablative transplantation (NMT) in NHL including in patients who had failed standard therapy or relapsed after prior autologous HSCT [28,70]. Thus, the exact role and optimal timing of NMT is an unanswered question that warrants further investigation. Phase II trials could initially best answer these questions. The lymphoma subtypes with dem-

onstrated sensitivity to a graft-versus-tumor (GVT) effect such as mantle cell lymphoma [71,72] and follicular cell lymphoma [73] are subtypes in which NMT should be explored. A multicenter Phase II study of NMT for relapsed follicular cell lymphoma is in an advanced stage of protocol development. Diffuse large cell lymphoma (DLCL) is the most common NHL subtype, and more options are needed for patients with recurrent DLCL who fail to demonstrate significant response to salvage chemotherapy. Thus, a prospective approach comparing autologous HSCT versus autologous followed by NMT could be considered if sufficient data existed to support the role of autologous followed by NMT for high-risk DLCL patients.

**Strategy 2.** Patients with T cell lymphomas typically respond to frontline therapy but relapse, commonly leading to shortened survivals despite the use of autologous HSCT as consolidation therapy in CRI or as a salvage therapy [74]. These observations underscore the need for investigation of allogeneic HSCT in this lymphoma subtype, but progress has been limited partly because of the low incidence and the heterogeneity of histologies in this particular NHL subtype. These problems could be addressed by the BMT CTN in a multi-institutional fashion.

**Strategy 3.** Demonstration of the role of autologous transplantation for the treatment of certain subsets of NHL such as mantle cell lymphoma or T cell lymphomas are attractive areas of study. For example, a randomized comparison between standard chemotherapy with HyperCVAD autologous HSCT could be pursued for the upfront treatment of mantle cell lymphoma.

### Discussion Summary

The major goal of future studies is to validate the role of autologous transplantation in the treatment of subsets of patients and to explore allogeneic transplantation for patients with high-risk disease. The biologic basis of the immune response and potential target antigens is of critical importance. Compilation of tissue samples for future immunologic analysis would be vital in achieving these goals. Additionally, the growing evidence implicating B cells in the pathogenesis of GVHD and cGVHD [75] supports the investigation of B cell depletion before, during, or after the conditioning regimen in assessing GVHD risk. Obstacles that hinder accrual of lymphoma patients to HSCT clinical trials include the heterogeneity of the disease and the availability of numerous nontransplant options. Lack of definitive response criteria and variability in intensity of NMT conditioning regimens are additional hurdles. Effectively harnessing the GVT responses with acceptable toxicity should be the inte-

gral goal of these trials. The advent of prognostic indices such as the IPI [8], FLIPI [76,77], FDG-PET scanning to assess response, and gene expression profiling [78] may further help identify which patients may most benefit from HSCT.

## COMMITTEE 9. MULTIPLE MYELOMA

### Current State of the Science

Although autologous HSCT has been shown to benefit patients with multiple myeloma (MM), the availability of new therapies has persuaded many patients and physicians that high-dose therapy (HDT) has a limited role as consolidation. Overcoming this barrier will require a concerted education effort. Significant knowledge gaps regarding the biology of myeloma and its treatment also hamper the efforts of developing rationale risk-tailored therapies.

### Trial I. The Role of Continued HDT with Autologous HSCT for All Symptomatic Myeloma Patients

*Background and Hypothesis.* MM is the most common indication for HDT with autologous HSCT [79]. The availability of new agents and combinations now result in CR and near CR rates of over 50% [80]. In this context, we will test the hypothesis that autologous HSCT will provide a survival advantage when used as early consideration as therapy for MM.

*Trial Design and Feasibility.* We propose a Phase III randomized trial for patients with newly diagnosed MM of early consolidation with HDT versus HDT upon relapse. Lack of consensus regarding optimal induction therapy as well as strong patient and physician preferences makes this study difficult to conduct. However, many cooperative groups are currently exploring the issue of optimal induction therapy for MM, and once these are concluded the role of consolidation therapy with ASCT can be reexplored. The BMT CTN is collaborating with ECOG and CALGB in a national trial to explore the role of posttransplant consolidation. Once this trial is concluded, we prepare to test the hypothesis that there is no benefit of tandem transplantation in the context of modern therapy for MM. This trial will randomize patients to receive 1 of 3 therapies after the first transplant: second autologous HSCT; 4 cycles of combination therapy with bortezomib, lenalidomide, dexamethasone, or observation. All patients will receive lenalidomide maintenance therapy.

**Strategy 1.** The Role for Allografting in Myeloma. The results of the recently published Italian study as well as the ongoing BMT CTN 0102 trial will help determine the role of allografting in MM [81].

The lack of sibling donors in most patients and the toxicity of this treatment modality will impede the use of allografting as frontline treatment in most patients. Because disease relapse remains the single most important cause of treatment failure in patients receiving RIC allografts for myeloma, allografting studies should focus on new graft-versus-myeloma targets, novel posttransplant strategies, as well as different conditioning regimens. Currently, a CIBMTR pilot trial of posttransplant lenalidomide maintenance is being designed and will begin later this year.

**Strategy 2.** The Use of CR as a Surrogate Marker for Long-Term Survival and Disease Control. The use of CR as an endpoint in MM trials is increasingly controversial [82]. Prospective evaluations of new molecular markers for specific cytogenetic abnormalities and other plasma cell indicators need to be incorporated into future trials.

### Discussion Summary

The SOSS participants felt that an early versus late transplant study was the most important question to address and encouraged the group to explore the idea again once an optimal induction treatment was identified. The participants also considered that continued study of allogeneic transplantation with curative intent should be a priority, particularly in younger patients or patients with high risk disease. Novel transplant strategies aimed at improving outcomes by reducing rates of relapse or severe cGVHD were also priorities. Finally, there was a general consensus that validation of the new response criteria for myeloma using samples from the current BMT CTN trial would be an important addition to our fund of knowledge.

## COMMITTEE 10. NONMALIGNANT DISORDERS

### Current State of the Science

Nonmalignant but life-threatening hematologic disorders such as AA, paroxysmal nocturnal hemoglobinuria, and thalassemia major have been treated with allogeneic HSCT for decades. Recently, there is significant interest in autologous HSCT as a therapy that could eliminate an individual's autoreactive lymphocytes in severe autoimmune disease such as systemic lupus erythematosus (SLE), multiple sclerosis (MS), and inflammatory bowel disease. In addition, investigators are exploring the potential of allogeneic HSCT to treat these same autoimmune diseases.

#### **Trial 1. GVHD Prophylaxis Using Mesenchymal Cells (MSC) in Matched-Related Donor Allogeneic Transplantation for Severe Aplastic Anemia**

*Background and Hypothesis.* Allogeneic HSCT can provide long-term disease control and potential

cure of nonmalignant diseases, including autoimmune diseases [81,83-86]. The main limitation to the application of allogeneic HSCT for the treatment of nonmalignant disorders is GVHD. MSC have immunomodulatory activity that may be beneficial in preventing GVHD and may also have a role in healing damaged tissue [87,88]. AA would be ideal as a model disease for testing the potential of MSC to prevent GVHD. We will test the hypothesis that administration of MSC will prevent GVHD and facilitate tissue repair after allogeneic HSCT for AA.

*Trial Design and Feasibility.* We propose a randomized Phase II trial of MSC infusion after HLA identical sibling donor HSCT for severe AA in an attempt to reduce the incidence of aGVHD from 50% to 25%. MSCs will be derived from the sibling donor, and serial determinations will document the persistence of donor-derived MSC in recipients. The optimal pretransplant conditioning regimen for AA (and unrelated donor HSCT) is currently being determined in the BMT CTN 0301 trial [89]. The proposed protocol would take advantage of the experiences from this trial and build on the existing protocol team's experience. To limit the heterogeneity of MSCs, common standard operating procedures (SOPs) will be developed and the cells produced by the NIH funded Production Assistance to Cell Therapy (PACT) facilities.

#### **Trial 2. CD 34 Selected Autologous HSCT for Severe Crohn's Disease**

*Background and Hypothesis.* Preliminary data suggest that Crohn's disease may also be amenable to therapy with autologous HSCT, which has shown promise in controlling several autoimmune diseases [90-92]. The mechanism of disease control is purported to be through resetting of the patient's immune system. Currently there are 3 national trials supported by the NIAID of autologous HSCT in patients with autoimmune diseases. Uncontrolled single-center data suggest efficacy for autologous HSCT in severe Crohn's disease [93,94], and a multinational trial is currently accruing patients in Europe. We will test the hypothesis that autologous HSCT may result in improved survival for poor prognosis inflammatory bowel disease.

*Trial Design and Feasibility.* We propose a randomized Phase II trial of autologous HSCT for therapy-refractory Crohn's disease using positively selected CD 34<sup>+</sup> peripheral blood progenitor cells (PBPC). Primary endpoints will be DFS, with secondary endpoints of OS, RRT, QOL, and disease. Crohn's disease activity (CDA) will be measured by the CDA index. Such an approach is currently being explored in Europe and the NIAID is very interested in this concept. Mortality in severe Crohn's disease is high, and gastrointestinal physicians would likely collaborate in

such an effort. Appropriately designed, a U.S. trial could be complementary to the current European trial but with sufficient commonality with regard to eligibility and outcome measures to allow interstudy comparisons or potentially a pooled analysis.

### Discussion Summary

During the discussion there was much enthusiasm for the future potential of mesenchymal cells in the area of allogeneic transplantation and regenerative medicine, although at present, the participants thought that the strategy was too early in development for a large network trial. There was also concern that HLA matched sibling donor transplants for AA may not be the best setting for such an early study as the outcomes are already very good despite GVHD and cGVHD. There was more enthusiasm for autologous HSCT in severe, refractory Crohn's disease with vigorous discussion of key issues such as eligibility, the conditioning regimen, and the role of CD34<sup>+</sup> selection. There was consensus to make preliminary enquiries of gastrointestinal physicians who currently manage such patients to determine their willingness to participate in such a trial.

## COMMITTEE II. GENE AND CELL THERAPY

### Current State of the Science

Randomized trials are currently ongoing using MSC to treat aGVHD and Thymidine Kinase (TK)-transduced T cells to augment immune recovery and treat relapse posttransplant. Global considerations with cell and gene therapy studies include multiple regulatory issues, including IND requirements, production of cells, clinical grade vectors and ancillary reagents, and manufacture of centralized versus multicenter cellular products. BMT CTN, in collaboration with other NHLBI resources such as PACT, can potentially support central administration, legal indemnification, clinical regulatory affairs, GMP vector manufacturing, and cell processing to facilitate advancement of these approaches. Cell therapy studies may extend traditional HSCT applications, and the BMT CTN could create a cellular therapy committee with the goal of fostering research across multiple transplant and nontransplant disciplines.

**Strategy 1. Immunotherapies.** Although multivirus specific CTLs have efficacy, the current methodology using repeated stimulation with APC cells expressing viral antigens is too cumbersome to use in multicenter trials [95]. Similar approaches using allodepleted T cells are still being optimized [96,97]. Alternative means of reconstituting antiviral immunity include rapid selection processes using tetramer selection or gamma-interferon capture,

but the former product has restricted specificity, whereas the latter is limited by low yields. Another option is to evaluate banked allogeneic lines, which could be manufactured with the assistance of PACT; a recent study showed activity of allogeneic Epstein-Barr virus (EBV)-specific CTL lines in patients with posttransplant lymphoma [98]. Transport of manufactured NK cell products has been validated, and thus a Minnesota regimen transferring haploidentical NK cells prior to a reduced intensity conditioning regimen may be ready for transfer to multicenter trials [99]. Tumor vaccine approaches using genetically modified cells have also shown activity posttransplant, and because a single bank can be made, this approach could feasibly be translated to BMT CTN. An alternative would be to develop a vaccination study using PR1 and WT1 peptides [100].

**Strategy 2. Gene Therapies.** The administration of donor lymphocyte infusions (DLI) post-HSCT is limited by the development of GVHD. Insertion of a conditional "suicide" gene (eg, HSV-TK) into the T cells prior to infusion allows them to be eliminated if they cause GVHD [101,102]. Multiple variations to this approach (vector, gene, and timing) may affect efficacy and need to be tested in clinical trials. The genes encoding the T cell receptors from antitumor CTL or chimeric molecules combining antibody elements that bind to tumor-associated antigens with intracellular signaling domains from T cell receptors can be inserted into mature T cells or into hematopoietic stem cells to engineer T cells with specific antitumor activity. Initial studies are focused on CD19 as a tumor-associated antigen of B lymphoid malignancies [103]. Several single-center trials of these approaches will open in the United States soon, but important logistic and legal issues will need to be resolved to move these studies from their single sites of origin to multiple sites. There are also a number of single-center studies exploring drug resistance gene therapy, a technology that could be used in future studies to improve allogeneic transplantation strategies.

**Strategy 3. Mesenchymal Cells.** The clinical application most amendable to a multicenter study is the use of MSCs to prevent/treat GVHD and/or to foster engraftment of hematopoietic stem cells [104,105]. Although the European Group for Blood and Marrow Transplant (EBMT) is currently conducting such studies, the MSCs are processed locally raising the possibility of heterogeneity of the MSC preparations among different institutions. A trial using homogeneous MSC population would advance the field, for example, in SAA where stable engraftment is a "cure," and GVHD/GVL is of no therapeutic value. Further, PACT could produce the MSCs for all sites using a

standardized isolation and expansion protocol that is free of fetal calf serum (FCS).

### Discussion Summary

The audience agreed that more preliminary single-center data are needed on the gene transfer approaches discussed before multicenter trials could be considered. They also felt that the setting of matched sibling transplant for nonmalignant disease may not be the best scenario to evaluate mesenchymal cells. Early relapse (eg, detectable minimal residual disease post-HSCT) was suggested as a good setting to assess the use of DLI with suicide gene for GVHD recall. There was support for a Phase II trial of allogeneic closely HLA-matched virus-specific CTLs to treat adenoviral infections.

## COMMITTEE 12. CLINICAL TRIAL DESIGN

### Current State of the Science

A major impediment to successful implementation and completion of clinical trials in HSCT (and other fields) is the amount of time and effort required to activate studies in individual institutions, to ensure compliance with often complex protocols and to complete and submit data for large numbers of required observations [106]. Funding for trials is often inadequate for these activities. The HSCT community should simplify HSCT protocols as much as possible and minimize the work required to participate, considering each of the following:

1. protocols should allow the use of institutional standards for nonessential selection criteria and clinical management practices;
2. the number and frequency of required observations should be limited to the minimum necessary to assess primary and secondary outcomes;
3. in deciding which secondary outcomes to assess, the potential value of the information obtained should be carefully weighed against the cost of obtaining it;
4. duplication of data collection should be avoided, and further consensus should be developed for HSCT-related common data elements to be used by all investigators planning clinical trials. Protocol-specific data collection instruments should build on the consensus datasets developed by CIBMTR and EBMT. These datasets have already been adopted by Foundation for Accreditation of Cellular Therapy (FACT) and the congressionally mandated SCTOD;
5. information systems that can interface with local and other network databases should be developed so that clinical data entered locally for institutional purposes can be used to comply with protocol-mandated data submission (“enter once, use often”

- principle); data submitted to the SCTOD should be shared with organizations doing clinical trials;
6. central institutional review board (IRB) review (rather than individual IRB review) should be encouraged;
7. improved accounting models should be developed to address the actual expense of conducting trials;
8. in developing trials, The BMT CTN should increase involvement of individuals/centers beyond the Steering Committee and Core Centers to ensure that issues of cost, feasibility, and relevance are better addressed and to enhance participation.

The use of combined Phase II-III designs would minimize the time spent activating trials. When Phase II and III trials are conducted separately, the Phase II trial is usually not randomized and compares an experimental therapy to a historical rate that may be either unknown or subject to selection bias [106-110]; enrolled patients cannot be used in a subsequent Phase III comparison. Additionally, the Phase III trial must go through a completely separate protocol development, review, and activation process. A seamless transition between Phase II and Phase III could increase efficiency by decreasing the total number of patients required and by avoiding the need for development, review and activation of a second protocol [111-115]. In the combined Phase II-III approach, a randomized Phase II stage employs a “screening” rule based on an unbiased comparison of the treatment and control arms; these criteria can include the planned primary endpoint for the Phase III portion of the trial, but may consider other endpoints. If screening criteria are met, the study moves into Phase III. Patients enrolled in the Phase II stage may be included in the Phase III comparison, possibly reducing the total sample size. One disadvantage is that more patients are needed for the Phase II stage of such trials than for single-arm Phase II trials. In selecting a design, it is important to consider (1) the reliability of the estimated historical rate, and (2) the amount of experience with the new treatment, because Phase II randomization may be more acceptable for a treatment with more extensive prior experience. A variation of the Phase II/III design uses group sequential methods in a Phase III study to accommodate early stopping for efficacy or futility.

### Discussion Summary

The audience was in general agreement with the recommendations, including simplifying protocols, broadening eligibility criteria, and permitting institutional standards for supportive care to the extent possible. It was felt that this would increase accrual and decrease the need for multiple amendments. The increasing complexity of the IRB and informed consent process and the need to simplify data reporting were also emphasized.

## CONCLUSIONS

The SOSS fully met expectations to frame the BMT CTN scientific agenda for the next several years. Following the presentation and discussion of all 12 committees, the Chairs, together with several of the international panel of experts, reviewed the discussions and made recommendations. High priority was given only to those protocols with sufficient preliminary data to begin protocol design and studies that awaited completion of ongoing trials were given lower priority. Of the 20 trials proposed, high enthusiasm was generally expressed for the following 11 protocols:

1. **GVHD:** Phase II trial of calcineurin-free regimens in patients with high risk cGVHD.
2. **QOL:** Phase III comparison of peritransplant stress management interventions.
3. **MM:** Phase III comparison of tandem transplant versus consolidation therapy with bortezomib, lenalidomide, dexamethasone, versus immediate maintenance therapy with lenalidomide in patients receiving 1 autotransplant of VRD as consolidation therapy for MM.
4. **AML:** Phase III comparison of chemotherapy versus unrelated donor in patients with high-risk AML in CR1.
5. **AML:** Phase III comparison of full intensity conditioning versus RIC in allogeneic HSCT recipients with AML aged 30-60 years.
6. **ALL:** Phase III comparison of chemotherapy + dasatinib versus allogeneic HSCT in patients with Ph+ ALL.
7. **CLL:** Phase II trial of reduced-intensity allogeneic HSCT in patients with very high-risk CLL.
8. **Lymphoma:** Phase II trial of reduced intensity allogeneic HSCT as primary therapy for T cell lymphoma.
9. **HLH:** Phase II trial of reduced intensity allogeneic HSCT in children with HLH.
10. **Nonmalignant diseases:** Phase II trial of autologous HSCT for refractory Crohn's disease.
11. **Cell therapy:** Phase II trial of HLA-matched, viral-specific CTLs to treat adenoviral infections.

The symposium leadership also unanimously recommended the formation of a Biomarkers Committee that would consider appropriate standardization of sample banks and potential processing across all network protocols. The search for biomarkers is proceeding in many other diseases and the BMT CTN will benefit from discussion and interchange with those groups on a regular basis.

### Committee 1

Claudio Anasetti  
(Chair)

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William Bensinger  
Dennis Confer

Ephraim Fuchs  
John Hansen  
Robertson Parkman  
John Wagner  
Edmund (Ned) Waller

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Stephen Emerson  
Mary E.D. Flowers  
Richard Jones  
Richard Maziarz  
Steven Pavletic  
David Porter  
Pavan Reddy  
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Michelle Bishop  
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Richard Champlin  
Stephen Couban  
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Hillard Lazarus  
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Martin Tallman

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Raymond Comenzo  
Nikhil Munshi  
S. Vincent Rajkumar  
Keith Stewart  
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Ronald Gress  
Kieren Marr  
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Stephan Grupp  
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Shelly Carter  
Dennis Confer  
Elihu Estey  
Nancy Geller  
Ted Gooley  
John Klein  
Brent Logan  
Paul Martin  
Eric Leifer

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