Biomarkers
Cell therapy
Quality of life

INTRODUCTION

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 conduct hematopoietic cell transplantation (HCT) clinical trials that would advance the standard of care for transplant patients. In preparation for this charter, the first State of the Science Symposium (SOSS) was convened that year. It defined 6 key areas that would 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/effect, and relapse of malignancy after HCT.

In 2007, the BMT CTN had been operational for 6 years, and it convened a second SOSS in Ann Arbor to frame the scientific agenda for the next 7 years. For that SOSS, the relapse of malignancy area was expanded to 3 committees: leukemia, lymphoma, and multiple myeloma (MM). Committees in pediatric diseases, nonmalignant diseases, cell and gene therapy, and trial design and implementation were also added. After the presentation and discussion of all 12 committees, the committee chairs, together with an international panel of experts, reviewed the symposium discussions and ranked the proposed trials. The group reached consensus regarding 11 questions to which it assigned highest priority. This article briefly reviews the status of each of those 11 topics and reflects on the current challenges and opportunities in BMT clinical research as we approach the third SOSS to be held at the end of February 2014 in Grapevine, Texas.

1. Phase II trial of calcineurin-free regimens in patients with high-risk chronic GVHD.

**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. Calcineurin inhibitors (CNIs) inhibit both regulatory T cells (Treg) and conventional T cells and may interfere with thymic function [1,2]. It is possible that observed rates of chronic GVHD relate to the inability of CNIs to induce long-term tolerance [3-5]. Augmentation of natural or inducible Treg number or function may mitigate GVHD and facilitate immune competence while maintaining the graft-versus-leukemia effect [6]. Several approaches to augment Treg numbers or activity are feasible. Sirolimus-based, CNI-free regimens (eg, sirolimus/mycophenolate mofetil) may foster Treg while inhibiting effector T cells. In mouse models, GVHD is prevented, whereas the graft-versus-leukemia effect is maintained [6]. Extracorporeal photopheresis also may enhance Treg numbers while modulating antigen presenting cell function. These observations led to the hypothesis that treatment without CNIs would improve outcomes for high-risk chronic GVHD patients.

**Trial Design and Feasibility.** The network designed two parallel phase II studies to lead into a single phase III study, with all patients receiving sirolimus as initial therapy. The phase II/III design was a strong recommendation of the Clinical Trials SOSS Committee. The phase II portion of the trial was completed in 2013, and the trial continues with a phase III component that compares sirolimus + prednisone to sirolimus + CNI + prednisone. This is 1 of only a very few phase III trials of initial treatment for high-risk chronic GVHD ever attempted. As of November 2013, patient accrual is on
target, with 140 of 300 patients, and is expected to be complete in early 2016.


Background and Hypothesis. Many studies have documented deficits in QOL after HCT, but few have tested interventions to improve QOL and functioning. Data from single centers suggest that exercise and stress management improves QOL and functional status in HCT recipients [7-13].

Trial Design and Feasibility. We designed a phase III randomized trial (BMT CTN 0902) to test the hypothesis that an exercise and stress management program would reduce fatigue and stress and improve QOL in HCT recipients. We compared usual care to a stress management intervention based on exercise and relaxation/imagination techniques in 710 patients. The primary endpoints were QOL and functional status at day 100 as measured by self-assessment. Accrual was extremely brisk and was completed within 21/2 years. Final results will be published later this year. Regardless of results, the demonstration that such studies can be completed rapidly in a multicenter setting using the BMT CTN infrastructure will encourage evaluation of future QOL interventions in HCT.

3. Phase III comparison of tandem autotransplant followed by lenalidomide maintenance versus consolidation therapy with bortezomib, lenalidomide, and dexamethasone followed by lenalidomide maintenance versus immediate maintenance therapy with lenalidomide in patients receiving a single autotransplant for MM.

Background and Hypothesis. MM is the most common indication for autologous HCT [14]. The availability of new agents and combinations now results in complete remission and near complete remission rates of over 50%, but best long-term survival is seen in protocols that include autologous transplantation as part of initial therapy [15]. The most appropriate post-transplant therapy to prolong both progression-free and overall survival is still undefined.

Trial Design and Feasibility. The Network designed a 3-arm trial (BMT CTN 0702) to test the hypothesis that there is no benefit of tandem transplantation in the context of modern post-transplant therapy for MM. Patients were randomized to receive 1 of 3 therapies after the first transplant: (1) second autologous HCT or (2) 4 cycles of combination therapy with bortezomib, lenalidomide, and dexamethasone or (3) observation. All patients received lenalidomide maintenance therapy. This 750-patient trial (250 per arm) completed accrual ahead of schedule in November 2013. An ancillary study (PRIMER) will evaluate 7 color flow cytometry to monitor residual disease by immunophenotype.


Background and Hypothesis. AML is the primary indication for unrelated donor transplantation, although many physicians defer this approach until after chemotherapy failure. Randomized trials and 2 meta-analyses have shown that HLA-identical sibling grafts improve survival compared with chemotherapy [16,17]. Survival of AML patients with high-risk cytogenetics transplanted in first remission is similar (45%), whether the donors are HLA-identical siblings or unrelated volunteers [18]. We will test the hypothesis that unrelated donor transplantation soon after induction chemotherapy improves survival of patients with AML compared with treatment with best chemotherapy.

Trial Design and Feasibility. The committee proposed a phase III trial comparing unrelated donor HCT to chemotherapy for AML patients with high-risk cytogenetics, aged 18 to 60 years. A Southwest Oncology Group (SWOG)-led collaboration among US cooperative groups recently initiated a trial (S2013) to test the hypothesis that it is possible to bring at least 60% of high-risk patients to allogeneic HCT in first complete remission with current donor availability.

5. Phase III comparison of full-intensity conditioning versus reduced-intensity conditioning (RIC) in allogeneic HCT recipients with AML aged 30 to 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 (30 to 60) years patients with AML is warranted.

Trial Design and Feasibility. We designed a randomized, 2-arm, phase III trial (BMT CTN 0901) to test the hypothesis that a reduction in the intensity of conditioning would decrease treatment-related mortality without increasing relapse, leading to a safer and equally effective regimen in patients ages 30 to 60 years with AML and myelodysplastic syndrome. Accrual to this 356-patient trial is ahead of target as of November 2013 and is expected to be complete in the summer of 2015.


Background and Hypothesis. Before the availability of imatinib and other BCR-ABL tyrosine kinase inhibitors, the outlook for patients with Ph+ acute lymphocytic leukemia treated with conventional chemotherapy was extremely poor, and, accordingly, allogeneic HCT was the treatment of choice. Several groups using imatinib in combination with conventional chemotherapy reported outcomes in Ph+ acute lymphocytic leukemia that rival those obtained with allogeneic HCT [19-21]. 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 similar to that achieved with allogeneic HCT.

Trial Design and Feasibility. Because this trial would evaluate patients at the time of diagnosis and include those who would not receive an allogeneic HCT, SWOG led the effort and followed the suggestion of this committee, designing a phase III, “biologic assignment” trial (S0805) in which patients either receive an allogeneic HCT in first complete remission if an appropriate donor was available or were treated with hyper-cyclophosphamide, vincristine, Adriamycin, dexamethasone (CVAD) and dasatinib. The trial met its accrual target of 100 patients in September 2013.

7. Phase II trial of reduced-intensity allogeneic HCT in patients with very high-risk chronic lymphocytic leukemia (CLL).
Background and Hypothesis. Approximately 25% of patients with CLL have aggressive disease with a shorter overall survival [22]. Preliminary results with RIC allogeneic HCT in patients with fludarabine-resistant CLL have yielded encouraging results [23].

Trial Design and Feasibility. In collaboration with Cancer and Leukemia Group B (CALGB) (now the Alliance), we designed a phase II trial to test the hypothesis that RIC allogeneic HCT will improve survival in patients with advanced CLL. The protocol team divided patients into 2 cohorts of 39 (early and advanced). As of November 2013, the advanced cohort had nearly finished accrual (35/39), but accrual in the early disease arm is considerably slower (14/39).

8. Phase II trial of reduced-intensity allogeneic HCT as primary therapy for peripheral T cell lymphoma.

Background and Hypothesis. Patients with peripheral T cell lymphomas typically respond to frontline therapy, but most patients ultimately relapse, leading to shortened survivals despite the use of autologous HCT as consolidation therapy in first complete remission or as a salvage therapy [24]. These observations underscore the need for investigation of allogeneic HCT in this lymphoma subtype. Progress has been limited partly because of the low incidence and the heterogeneity of histologies in this particular non-Hodgkin lymphoma subtype.

Trial Design and Feasibility. The BMT CTN worked closely with CALGB for 3 years in the design of this trial (CALGB 100901), but the effort was discontinued because of the rarity of the disease and the low likelihood that the trial could complete accrual.

9. Phase II trial of reduced-intensity allogeneic HCT in children with hemophagocytic lymphohistiocytosis (HLH).

Background and Hypothesis. Hemophagocytic disorders comprise primarily HLH but include X-linked lymphoproliferative syndrome, 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-α. The diagnosis of HLH can be established by genetic and functional testing. Allogeneic HCT is the only curative option, but a major barrier to success is 35% treatment-related mortality associated with intensive conditioning regimens [25].

Trial Design and Feasibility. We designed a multicenter, phase II trial (BMT CTN 1204) of 35 patients to test the hypothesis that RIC will result in improved survival by decreased treatment-related mortality without loss of efficacy for patients with HLH. Pilot data [26,27] suggest that an RIC regimen is safe and effective in children with nonmalignant disorders, including HLH. Accrual began at the end of 2013 and is expected to last 3 years.


Background and Hypothesis. Preliminary data suggest that Crohn's disease may also be amenable to therapy with autologous HCT, which has shown promise in controlling several autoimmune diseases [28-30]. The mechanism of disease control is purported to be through resetting of the patient's immune system. Currently, 3 national trials are supported by the National Institute of Allergy and Infectious Diseases of autologous HCT for autoimmune diseases. Uncontrolled single-center data suggest efficacy for autologous HCT in severe Crohn's disease [31,32]. A multinational trial is currently accruing patients in Europe.

Trial Design and Feasibility. We proposed to test the hypothesis that autologous HCT with positively selected CD34+ peripheral blood progenitor cells would result in improved survival for patients with severe Crohn's disease in a multicenter phase II trial. The feasibility of this trial was questioned almost immediately because HCTs occur only rarely for this and other autoimmune diseases in the United States, in large part because of the difficulty in obtaining insurance coverage for the clinical costs of these procedures. The trial was never initiated.


Background and Hypothesis. Although multivirus-specific cytotoxic T lymphocytes have proven efficacy, the current methodology using repeated stimulation with antigen presenting cells expressing viral antigens is too cumbersome to use in multicenter trials [33]. Similar approaches using allogeneic or depleted T cells are still being optimized [34,35]. Alternative means of reconstituting antiviral immunity include rapid selection processes using tetramer selection or γ-interferon capture, but the former restricts specificity, whereas the latter produces low yields. Another option is banked allogeneic lines, which could be manufactured with the assistance of the Production Assistance for Cellular Therapies program; a study used allogeneic Epstein-Barr virus–specific cytotoxic T lymphocytes lines in patients with post-transplant lymphoma [36].

Trial Design and Feasibility. Using protocol templates and case report forms from the BMT CTN, the Production Assistance for Cellular Therapies program led a phase II multicenter study of banked allogeneic trivirus-specific T cells for 50 allogeneic HCT recipients with resistant cytomegalovirus, adenoviral, or Epstein-Barr virus infection (NCT00711035). The trial was sponsored by the NHLBI, accrual was completed in 2011, and its results were published last year. Sponsored by NIHBLI, completed accrual in 2011. Its results were published last year [37].

The last SOSS also unanimously recommended that the BMT CTN form 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 would benefit from discussion and interchange with those groups on a regular basis. Not only did the network form such a committee, which now reviews the biospecimen collection in all new protocols, the committee designed an additional trial to establish a cohort of prospectively collected biologic samples from 1500 patients (BMT CTN 1202) to be a shared resource for future allogeneic HCT trials. Accrual is extremely brisk and well ahead of projections, with completion estimated in 2½ years.

Thus, 9 of the 11 trials recommended were launched; 4 have already completed patient accrual, and 5 are ongoing. Two were never launched because a more careful analysis determined they were infeasible. During this time, the Network also completed 9 protocols recommended by the initial SOSS in 2001 and continued or launched an additional
10 trials, some in collaboration with other networks, publishing 26 peer-reviewed papers with several more currently under review. This remarkable record of achievement, which includes the accrual of almost 4000 patients to 25 clinical trials in the past 6 years, is due to several important factors. Perhaps the most important is the NIH collaboration that enabled the establishment of the BMT CTN: both NHLBI and NCI have jointly supported the BMT CTN from its initiation. The issues addressed by the BMT CTN include priority areas for both Institutes, and the network’s ability to successfully address them has been greatly enhanced by inter-Institute cooperation and resource-sharing, including emendation of NIH policies and procedures to accelerate the design and implementation of important trials. This culture of collaboration extends to other Networks and protocol team members who frequently face shifting priorities, lack of access to new drugs, and elusive clinical equipoise in their search for the common ground needed for successful protocols.

A second instrumental factor is the strong and steady leadership of the BMT CTN Steering Committee, with its constant efforts to harmonize efforts within the Network as well as its commitment to work effectively with the NCI cooperative groups and other networks and consortia. A third key factor was the transparency, inclusiveness, and external validation of the 2007 SOSS process itself. 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. Additionally, members of the NCI cooperative groups were included in all the malignancy committees (leukemia, lymphoma, MM) and several other committees. A panel of external international experts evaluated all the recommendations and led vigorous question periods after each committee presentation. All these factors led to a remarkable consensus at the end of the conference. The 2007 symposium has served as the template for the upcoming meeting in Texas, which we expect to represent a milestone in the success of the Network.

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REFERENCES


