Biol Blood Marrow Transplant 20 (2014) 149–153

Report

Blood and Marrow Transplant Clinical Trials Network: Progress since the State of the Science Symposium 2007

James L.M. Ferrara*

Department of Pediatrics, University of Michigan, Ann Arbor, Michigan

Article history:
Received 7 November 2013
Accepted 7 November 2013

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
Hemaphogocytic lymphohistiocytosis
Crohn's disease
Cell therapy
Biomarkers
Quality of life

A B S T R A C T

Outcomes of hematopoietic cell transplantation continue to improve. New techniques have reduced transplant toxicities, and there are new sources of hematopoietic stem cells from related and unrelated donors. In June 2007, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) convened a State of the Science Symposium (SOSS) in Ann Arbor and identified 11 high priority clinical trials for the network to pursue. This article reviews both the status of those trials and the record of achievement of the BMT CTN as it convenes another SOSS in Grapevine, Texas in February 2014.

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/late effects, 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

Financial disclosure: See Acknowledgments on page 152.

* Correspondence and reprint requests: James L.M. Ferrara, MD, 1500 E. Medical Center Dr., 6308 Cancer Center, Ann Arbor, MI 49109.
E-mail address: ferrara@umich.edu.

1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.11.006

target, with 140 of 300 patients, and is expected to be complete in early 2016.

2. Phase III comparison of peritransplant stress management interventions on quality of life (QOL).

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/imagery 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 $2^1/_2$ 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 lenalinomide 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.

4. Phase III comparison of chemotherapy versus unrelated donor HCT in patients with high-risk acute myeloid leukemia (AML) in first complete remission.

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.

6. Phase III comparison of chemotherapy + dasatinib versus allogeneic HCT in patients with Ph+ acute lymphocytic leukemia.

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 received 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).