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The Blood and Marrow Transplant Clinical Trials Network: An Effective Infrastructure for Addressing Important Issues in Hematopoietic Cell Transplantation

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A B S T R A C T

Hematopoietic cell transplantation (HCT) is a rapidly evolving field with active preclinical and clinical development of new strategies for patient assessment, graft selection and manipulation, and pre- and post-transplantation drug and cell therapy. New strategies require evaluation in definitive clinical trials; however, HCT trials face unique challenges, including the relatively small number of transplantations performed at any single center, the diverse indications for HCT requiring dissimilar approaches, the complex nature of the intervention itself, the risk of multiple complications in the immediate post-transplantation period, and the risk of important, though infrequent, late effects. The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) was established by the US National Heart Lung and Blood Institute and the National Cancer Institute to meet these challenges. In its 15 years as a network, the BMT CTN has proven to be a successful infrastructure for planning, implementing, and completing such trials and for providing definitive answers to questions leading to improvements in the understanding and practice of HCT. It has opened 37 trials, about one-half phase 2 and one-half phase 3, enrolled more than 8000 patients, and published 57 papers addressing important issues in the treatment of patients with life-threatening malignant and nonmalignant blood disorders. This review describes the network's accomplishments, key components of its success, lessons learned over the past 15 years, and challenges for the future.

INTRODUCTION

About 21,000 hematopoietic cell transplantations (HCTs) will be performed in the United States in 2016 and 65,000 will be performed worldwide (Center for International Blood and Marrow Transplant Research, unpublished data). HCT is a rapidly evolving field with active preclinical and clinical development of new approaches to patient assessment, graft selection and manipulation, and pre- and post-transplantation drug and cell therapy. New diagnostic and therapeutic strategies require evaluation in definitive clinical trials as does the role of HCT versus other therapies. However, HCT trials face unique challenges, including the relatively small number of transplantations performed at any single center, the diverse indications for HCT requiring dissimilar approaches, the complex nature of the intervention itself, the risk of multiple complications in the immediate post-transplantation period, and the risk of important, though infrequent, late effects. Although there is a longstanding mechanism for investigators to collaboratively conduct observational HCT studies in the United States using data collected by the Center for International Blood and Marrow Transplant Research (CIBMTR), the ability to collaboratively develop and implement multicenter interventional HCT trials was long hampered by limited funding, by the low priority afforded to HCT trials both by networks focused on non-HCT cancer therapy and by pharmaceutical companies, and by lack of an effective multicenter HCT trials infrastructure [1,2].

To address this need, in 2001, the National Institute of Health's (NIH) National Heart, Lung, and Blood Institute (NHLBI) and National Cancer Institute (NCI) issued a Request for Applications (RFA) (HLA-01-004), inviting participation in a Blood and Marrow Transplant Clinical Trials Network

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(BMT CTN). The objective of the RFA was to establish and maintain the necessary infrastructure to conduct large, multi-institutional clinical trials to improve HCT outcomes. The mandate was to execute large phase 2 and 3 trials with broad national participation. In its 15 years as a network, the BMT CTN has proven to be a successful infrastructure for planning, implementing, and completing such trials, providing definitive answers to questions that have led to improvements in the understanding and practice of HCT. It has opened 37 trials addressing important issues in the treatment of patients with life-threatening malignant and nonmalignant blood disorders. These trials, about one-half phase 2 and one-half phase 3, with a median enrollment of 180 (range, 17 to 1700), address issues of donor availability, engraftment, graft-versus-host disease (GVHD), post-transplantation infection, disease control, organ toxicity, cost-effectiveness, and quality of life. The goal is to make HCT a therapy that is more universally available (by expanding donor sources and allowing use in older, sicker patients), safer (by reducing regimen-related toxicity, life-threatening infection, and GVHD), and effective (by various strategies to prevent relapse). Illustrative studies and findings are listed in Table 1.

Numerous advances substantially changed the landscape of HCT over the decade and one-half since establishment of the BMT CTN, and BMT CTN trials played a key role in developing many of them, building on preclinical and early clinical work being done in its member centers and elsewhere. In the early days of the BMT CTN, complications of HCT, especially GVHD, limited the effectiveness and availability of the procedure. Nearly one-half of the patients in need of HCT, including most patients in ethnic minority groups, particularly African-Americans, were denied the procedure because they did not have available matched donors. Older and less fit patients were deemed to not be candidates for HCT because of toxicity concerns. BMT CTN–led trials evaluating use of unrelated umbilical cord blood and related haploidentical donor transplantation after reduced-intensity conditioning confirmed the safety and effectiveness of these alternative allograft sources in the multicenter setting, with results close to those seen with HLA-matched donors [16]. The BMT CTN, working collaboratively with the NCI-supported cooperative group The Alliance for Clinical Trials in Oncology (previously CALGB), also validated single-center data that reduced-intensity conditioning allows allogeneic HCT to be used effectively in patients with acute myeloid leukemia (AML) older than 60 years, with either an HLA-identical sibling or unrelated donor [19]. These studies helped expand applicability of HCT to many more patients with both malignant and nonmalignant blood disorders, including patients in their 70s. Additionally, >30% of participants in the ongoing BMT CTN phase 3 trial randomized to either unrelated umbilical cord blood or related haploidentical allografts are from ethnic minority groups, and patients into their 70s are eligible.

The availability and effectiveness of HCT make it an important platform for incorporating novel therapies. HCT not only provides a state of minimal residual disease but, in the case of allografting, also a new nontolerant immune system. The BMT CTN is at the forefront of trials combining HCT with novel therapeutics. Its collaboration with the Alliance to complete a randomized trial of lenalidomide maintenance after HCT for multiple myeloma, a trial almost closed for poor accrual before BMT CTN's participation, proved to be practice changing [18]. A trial adding a dendritic cell vaccine to post-transplantation maintenance in this setting is about to be launched. These and other studies represent a next generation of BMT CTN trials studying post-HCT strategies to improve response and reduce relapse (see below).

NETWORK STRUCTURE

The initial structure funded 16 clinical core centers, geographically distributed throughout the United States; several of these core centers were consortia of 2 or more institutions. The Data and Coordinating Center (DCC) is a consortium of 3 organizations, each with extensive experience in HCT: the CIBMTR, the Emmes Corporation, and the National Marrow Donor Program (NMDP)/Be The Match. The CIBMTR is a collaborative research program of the Medical College of Wisconsin, Milwaukee, and NMDP/Be The Match, Minneapolis, with offices on both campuses. Non-CIBMTR departments of NMDP/Be The Match handle contracts and finances for the network. The Emmes Corporation is a contract research organization in Rockville, Maryland that managed 2 previous national HCT trials funded by NHLBI: the T Cell Depletion Trial in Unrelated Donor Marrow Transplantation [24] and the Cord Blood Transplantation Trial [25]. The DCC grant was awarded to the Medical College of Wisconsin with subcontracts to NMDP/Be The Match and Emmes. Today the BMT CTN is in its third grant cycle. Although subsequent cycles brought some changes, including increasing the number of core centers to 20, the basic structure is the same (Figure 1).

The BMT CTN steering committee sets the scientific agenda and oversees selection, design, execution, and analysis of all BMT CTN studies. The BMT CTN steering committee includes the principal investigator of each core center or consortium and the DCC, the NHLBI project officer, the NCI project officer, a representative of each of the NCI-funded cooperative groups, and representatives of affiliate centers that meet standards for exemplary participation in BMT CTN trials.

Protocols are developed by protocol teams, each composed of 2 or more protocol cochairs, 5 to 7 other investigators, an NHLBI and an NCI representative, a DCC protocol officer, who is a medical doctor with clinical trials training and experience, a DCC protocol coordinator, a DCC statistician, and an NHLBI statistician. Protocol development begins after a concept (presented at a very early stage of development) is accepted by the steering committee and is facilitated by weekly conference calls and, recently, by 1 or more in-person meetings of the protocol team.

Independent review committees appointed by NHLBI provide additional oversight for BMT CTN trials. The protocol review committee evaluates each study for scientific merit and 2 data and safety monitoring boards are each responsible for about one-half of the network portfolio. Each of these includes a chair and members with expertise in biostatistics, clinical trials, bioethics, HCT, and specific disease areas of network studies.

ACCOMPLISHMENTS

Since launching its first trial in November 2003, the BMT CTN has an outstanding record of accomplishments. A few (current through October 2015) are listed below:

- The network opened 37 clinical trials addressing important issues in the treatment of patients with life-threatening blood disorders; to date, the network has enrolled >8300 participants from >120 centers on these trials.
  BMT CTN was the lead group for 30 trials; 5 were developed in collaboration with other NIH-funded groups, and