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Report

Blood and Marrow Transplant Clinical Trials Network State of the Science Symposium 2014

Frederick R. Appelbaum [1,*], Claudio Anasetti [2], Joseph H. Antin [3], Harold Atkins [4], Stella Davies [5], Steven Devine [6], Sergio Giralt [7], Helen Heslop [8], Ginna Laport [9], Stephanie J. Lee [1], Brent Logan [10], Marcelo Pasquini [10], Michael Pulsipher [11], Edward Stadtmauer [12], John R. Wingard [13], Mary M. Horowitz [10]

[1] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[2] *Research & Clinical Trials, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida*
[3] *Stem Cell Transplants, Dana-Farber Cancer Institute, Boston, Massachusetts*
[4] *Cancer Therapeutics Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada*
[5] *Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital, Cincinnati, Ohio*
[6] *Blood and Marrow Transplant Program, The Ohio State University, Columbus, Ohio*
[7] *Bone Marrow Transplant Service, Memorial Sloan-Kettering Cancer Center, New York, New York*
[8] *Adult Bone Marrow and Stem Cell Transplant Program, Baylor College of Medicine, Houston, Texas*
[9] *Medicine—Blood & Marrow Transplantation, Stanford Hospital and Clinics, Stanford, California*
[10] *Clinical Research Division, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin*
[11] *Biostatistics, University of Utah School of Medicine, Primary Children's Hospital, Salt Lake City, Utah*
[12] *Division of Hematology and Oncology, University of Pennsylvania, Philadelphia, Pennsylvania*
[13] *Hematology Division—Internal Medicine Department, University of Florida, Gainesville, Florida*

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INTRODUCTION

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) was chartered by the National Heart, Lung, and Blood Institute and the National Cancer Institute (NCI) in 2001 to conduct clinical trials aimed at improving the outcome of patients undergoing hematopoietic cell transplantation (HCT). Since its inception, activities of the BMT CTN have been guided by a series of State of the Science Symposia (SOSS), conducted to determine the most important and clinically relevant questions to be addressed by the cooperative activities of the Network. The first State of the Science Symposium identified 6 major questions that the BMT CTN should consider (see Table 1). Over the following 6 years, the BMT CTN activated 12 trials that addressed most of these questions, as well as others, and accrued more than 2000 patients to these trials. In 2007, a second SOSS (SOSS2) identified a new series of 11 clinically important questions (see Table 1) [1]. Since SOSS2, the BMT CTN has developed and activated 7 studies addressing these issues, 6 of which have completed accrual; accrual continues to the remaining study. The NCI cancer cooperative groups developed and activated 2 additional trials endorsed by the BMT CTN addressing these questions, 1 of which has completed accrual with 1 ongoing. Studies addressing the final 2 SOSS2 questions were not initiated after further analysis determined that they were likely not feasible at this time. Overall, the BMT CTN has activated 33 trials addressing many of the most pressing questions facing the HCT community, has accrued >6700 patients to trials, and has published results in 37 manuscripts, including many high-impact, practice-changing papers [2].

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* Correspondence and reprint requests: Frederick R. Appelbaum, MD, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, D5-310, Seattle, WA 98109.
E-mail address: fappelba@fhcrc.org (F.R. Appelbaum).

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Table 1
Clinical Research Questions Identified at SOSS

First SOSS
1. Bone marrow versus peripheral blood for matched sibling HCT
2. Bone marrow versus peripheral blood for matched unrelated donor HCT
3. Single versus double cord blood transplantation
4. Utility of T cell depletion of allogeneic bone marrow
5. Utility of sirolimus added to conventional GVHD prophylaxis
6. Allogeneic transplantation versus chemotherapy for older patients with AML

SOSS2
1. Chemotherapy versus unrelated donor HCT for patients with high-risk AML
2. Full intensity versus reduced intensity conditioning for patients with AML
3. Chemotherapy + dasatinib versus allogeneic HCT for patients with Ph+ ALL
4. Reduced intensity allogeneic HCT for patients with very high-risk CLL
5. Reduced intensity allogeneic HCT for T cell lymphoma
6. Reduced intensity allogeneic HCT in children with hemophagocytic lymphohistiocytosis
7. Autologous HCT for refractory Crohn's disease
8. Use of viral specific T cells to treat adenoviral infections
9. Development of calcineurin-free regimens to treat chronic GVHD
10. Comparison of allogeneic HCT versus chemotherapy after autologous HCT for patients with MM
11. Comparison of peritransplantation stress management interventions

Ph+ indicates philadelphia chromosome positive; CLL, chronic lymphocytic leukemia.

The BMT CTN held its third SOSS meeting in February 2014 to set a scientific agenda for the coming half decade. Given the success of the previous 2 SOSS meetings, the 2014 SOSS followed a similar format. Briefly, approximately 9 months before the meeting, a BMT CTN planning group formed 13 committees (similar to those in SOSS2) addressing 13 major topics in HCT, and the planning group named committee chairs and members for each committee. Committee members included cooperative group leaders, representatives from specialized programs of research excellence, individual cancer center leaders, and laboratory-oriented investigators and clinical trialists. To encourage diverse views and gain the broadest possible perspective, no individual was permitted to serve on more than 1 committee. Additionally, 2 external reviewers, who were not active participants in BMT CTN activities or centers, were identified for each committee. The planning group, committee chairs, members, and external reviewers are listed in Table 2. Each committee was charged with identifying up to 3 of the most important clinical questions in their area that could be addressed by the BMT CTN in the next few years. The committees met multiple times over the ensuing 6 months to develop their list and to create brief documents describing the outcomes of their deliberations. These reports were circulated to the SOSS planning group, the other committee chairs, and the external reviewers before the SOSS meeting. Participation in the SOSS meeting was open to the public and approximately 350 individuals attended. At the meeting, each committee chair presented his or her group's report, following which the external reviewers presented their views. A discussion period followed each presentation; these discussions were open to all in attendance. At the conclusion of the public meeting, the planning committee, committee chairs, and external reviewers met, modified, and prioritized the study concepts, based on the SOSS meeting discussions. This article summarizes the individual committee reports and a list of those trials most enthusiastically endorsed by the symposium leadership.

COMMITTEE 1: LEUKEMIA

Current State of the Science

Leukemia is the most common indication for allogeneic HCT and disease recurrence is the most common reason for transplantation failure. Relapse occurs most frequently early after transplantation before full donor immune reactivity has occurred. Accordingly, this committee chose to focus primarily on strategies to mitigate the risk of relapse in acute myeloid leukemia (AML) after HCT based on the availability of new agents, encouraging preliminary data, and trial feasibility. The committee also noted that the role of allogeneic HCT in older patients remains unsettled.

Strategy 1: A Randomized, Double-blind, Phase III Study of Fms-like tyrosine Kinase 3 (FLT3) Inhibition Compared with Placebo as Maintenance Therapy in Subjects with FLT3–internal Tandem Duplication (ITD)$^+$ AML Who Are in Remission after Allogeneic HCT

Hypothesis

The continued administration of FLT3 inhibition in patients with FLT3-ITD$^+$ AML in remission after HCT is feasible and will prevent early relapse leading to improved leukemia-free survival compared with placebo.

Background

Approximately 20% to 30% of patients with AML harbor an ITD mutation in the FLT3 receptor that results in a high risk of relapse after conventional chemotherapy [3]. Retrospective data suggest such patients may benefit from HCT, yet the risk of relapse after HCT is still high [4]. Agents that inhibit FLT3 signaling are available and have been tested in clinical trials [5].

Trial design

The committee proposed a phase III, randomized, double-blind, 2-arm study to determine the clinical benefit of FLT3 inhibitor monotherapy compared with placebo for patients with FLT3-ITD$^+$ AML who are in remission after HCT. The primary endpoint would be leukemia-free survival with a sample size based on a comparison of the 2 arms. A hazard ratio of .6 was suggested.

Feasibility and logistics

This trial design would be definitive but would require a large sample size (~500 patients) and thus necessitate a multicenter and, possibly, multinational effort with support from 1 of the drug manufacturers. At this time, quizartinib appears to be the most promising agent, based on preliminary efficacy data [5].

Strategy 2: A Randomized, Phase III Study of Low-dose Azacitidine Maintenance Compared with no Maintenance in Patients with AML or Myelodysplastic Syndromes at High Risk of Relapse after HCT

Hypothesis

Post-transplantation low-dose azacitidine maintenance will decrease the risk of relapse after allogeneic HCT for AML and or myelodysplastic syndromes (MDS).

Background

The hypomethylating agents 5-azacitidine (AZA) and decitabine are clinically active against both MDS and AML [6]. In particular, AZA prolongs survival compared with