Biol Blood Marrow Transplant 21 (2015) 1815–1822

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Clinical Research: Analysis

Comparison of Characteristics and Outcomes of Trial Participants and Nonparticipants: Example of Blood and Marrow Transplant Clinical Trials Network 0201 Trial

Nandita Khera [1,*], Navneet S. Majhail [2], Ruta Brazauskas [3,4], Zhiwei Wang [3], Naya He [3], Mahmoud D. Aljurf [5], Görgün Akpek [6], Yoshiko Atsuta [7,8], Sara Beattie [9], Christopher N. Bredeson [10], Linda J. Burns [11], Jignesh D. Dalal [12], César O. Freytes [13], Vikas Gupta [14], Yoshihiro Inamoto [15], Hillard M. Lazarus [16], Charles F. LeMaistre [17], Amir Steinberg [18], David Szwajcer [19], John R. Wingard [20], Baldeep Wirk [21], William A. Wood [22], Steven Joffe [23], Theresa E. Hahn [24], Fausto R. Loberiza [25], Claudio Anasetti [26], Mary M. Horowitz [3], Stephanie J. Lee [27]

[1] *Department of Hematology/Oncology, Mayo Clinic, Phoenix, Arizona*
[2] *Blood and Marrow Transplant Program, Cleveland Clinic, Taussig Cancer Institute, Cleveland, Ohio*
[3] *Center for International Blood and Marrow Transplant Research, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*
[4] *Division of Biostatistics, Institute of Health and Society, Medical College of Wisconsin, Milwaukee, Wisconsin*
[5] *Department of Oncology, King Faisal Specialist Hospital Center and Research, Riyadh, Saudi Arabia*
[6] *Section of Hematology Oncology, Banner MD Anderson Cancer Center, Gilbert, Arizona*
[7] *Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan*
[8] *Nagoya University Graduate School of Medicine, Nagoya, Japan*
[9] *School of Psychology, University of Ottawa, Ottawa, Ontario, Canada*
[10] *Ottawa Hospital Blood and Marrow Transplant Program and the Ottawa Hospital Research Institute, Ottawa, Ontario, Canada*
[11] *Health Services Research, National Marrow Donor Program/Be The Match, Minneapolis, Minnesota*
[12] *Bone Marrow Transplantation, Pediatric Hematology/Oncology, The Children's Mercy Hospitals and Clinics, Kansas City, Missouri*
[13] *South Texas Veterans Health Care System and University of Texas Health Science Center San Antonio, San Antonio, Texas*
[14] *Blood and Marrow Transplant Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada*
[15] *Division of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan*
[16] *Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, Ohio*
[17] *Hematology and Bone Marrow Transplant, Sarah Cannon, Nashville, Tennessee*
[18] *Department of Hematology-Oncology, Mount Sinai Hospital, New York, New York*
[19] *Department of Hematology, CancerCare Manitoba/University of Manitoba, Winnipeg, Manitoba, Canada*
[20] *Division of Hematology and Oncology, Department of Medicine, University of Florida, Gainesville, Florida*
[21] *Department of Internal Medicine, Stony Brook University Medical Center, Stony Brook, New York*
[22] *Division of Hematology/Oncology, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina*
[23] *Department of Medical Ethics and Health Policy, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania*
[24] *Department of Medicine, Roswell Park Cancer Institute, Buffalo, New York*
[25] *Department of Internal Medicine, Nebraska Medical Center, Omaha, Nebraska*
[26] *Bone Marrow Transplant Program, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida*
[27] *Clinical Transplant Research, Fred Hutchinson Cancer Research Center, Seattle, Washington*

Article history:
Received 13 May 2015
Accepted 4 June 2015

Key Words:
Trial participation
Hematopoietic cell transplantation

A B S T R A C T

Controversy surrounds the question of whether clinical trial participants have better outcomes than comparable patients who are not treated on a trial. We explored this question using a recent large, randomized, multicenter study comparing peripheral blood (PB) with bone marrow transplantation from unrelated donors, conducted by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). We compared characteristics and outcomes of study participants (n = 494) and nonparticipants (n = 1384) who appeared eligible and received similar treatment without enrolling on the BMT CTN trial at participating centers during the study time period. Data were obtained from the Center for International Blood and Marrow Transplant

Financial disclosure: See Acknowledgments on page 1821.

* Correspondence and reprint requests: Nandita Khera, MD MPH, Assistant Professor of Medicine, College of Medicine, Mayo Clinic, 5777 E. Mayo Boulevard, Phoenix, AZ 85054.
E-mail address: khera.nandita@mayo.edu (N. Khera).

http://dx.doi.org/10.1016/j.bbmt.2015.06.004
1083-8791/

Research. Outcomes were compared between the 2 groups using Cox proportional hazards regression models. No significant differences in age, sex, disease distribution, race/ethnicity, HLA matching, comorbidities, and interval from diagnosis to hematopoietic cell transplantation were seen between the participants and nonparticipants. Nonparticipants were more likely to have lower performance status, lower risk disease, and older donors, and to receive myeloablative conditioning and antithymocyte globulin. Nonparticipants were also more likely to receive PB grafts, the intervention tested in the trial (66% versus 50%, $P < .001$). Overall survival, transplantation-related mortality, and incidences of acute or chronic graft-versus-host disease were comparable between the 2 groups though relapse was higher (hazard ratio, 1.22; 95% confidence interval, 1.02 to 1.46; $P = .028$) in nonparticipants. Despite differences in certain baseline characteristics, survival was comparable between study participants and nonparticipants. The results of the BMT CTN trial appear generalizable to the population of trial-eligible patients.

INTRODUCTION

Randomized clinical trials (RCT) are considered the gold standard in clinical research. However, their applicability to larger populations may be limited because trial patients may not be representative of most patients because of selection bias [1]. Despite this potential limitation, very few trials have the generalizability of their results assessed, even though discussion about generalizability is a quality indicator for RCT reporting within the Consolidated Standards of Reporting Trials guidelines [2]. It is also controversial whether patients enrolled in trials have better outcomes than those not enrolled in trials, controlling for biological characteristics. Although some studies show improved outcomes in trial participants compared with nonparticipants [3-6], others report no trial effect [7,8]. Peppercorn et al. reported that most studies comparing outcomes between trial and nontrial participants failed to control for potential confounding factors between the groups, and, therefore, available evidence does not support a trial effect on outcomes [9].

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) conducts multicenter trials to improve treatment approaches in hematopoietic cell transplantation (HCT). A phase III randomized, multicenter study conducted by BMT CTN (BMT CTN 0201) between March 2004 and September 2009 compared outcomes after bone marrow (BM) and filgrastim-mobilized peripheral blood (PB) HCT from unrelated donors (URD) [10]. The trial found no significant difference in survival between the 2 groups, but it found a significant increase in the risk of chronic graft-versus-host disease (GVHD) with PB. Its practice-changing potential is based on the fact that the study supports the use of BM grafts with decreased chronic GVHD, in the current era when PB is used in 70% of URD transplantations.

Before applying the study results to clinical practice, it is important to understand their generalizability to the universe of potential patients. To do so, we compared the characteristics and outcomes of participants in BMT CTN protocol 0201 with those of patients receiving URD HCTs at the same centers during the study time period but who were not study participants, using data from the Center for International Blood and Marrow Transplant Research (CIBMTR). We restricted the analysis to centers participating in BMT CTN and to patients receiving similar treatment off-protocol to minimize confounding variables while assessing for a trial effect.

PATIENTS AND METHODS

Data Source

The CIBMTR is a research collaboration of the Medical College of Wisconsin and the National Marrow Donor Program/Be The Match. More than 350 transplantation centers worldwide contribute detailed data on consecutive allogeneic and autologous HCT to the CIBMTR's outcomes registry. The CIBMTR also leads the data coordinating center for the BMT CTN. Patients are followed longitudinally with yearly follow-up. Compliance is monitored by on-site audits. Observational studies by the CIBMTR are performed in compliance with the Privacy Rule (Health Insurance Portability and Accountability Act) as a Public Health Authority and with all applicable federal regulations pertaining to the protection of human research participants as determined by continuous review of the institutional review board of the National Marrow Donor Program.

The current study included 2 main cohorts of patients for whom information was retrieved from the CIBMTR database: patients treated on the BMT CTN 0201 protocol and patients who underwent URD transplantations during the study time period at 38 participating centers but who were not on the BMT CTN study. The eligibility criteria for the BMT CTN protocol included age $<$ 66 years and HCT for acute leukemia, myelodysplasia, chronic myeloid or myelomonocytic leukemia, or myelofibrosis. Exclusion criteria are included in Supplementary Table 1.

The comparator group of interest was patients who, based on information from the CIBMTR database, appeared eligible per the inclusion and exclusion criteria of the BMT CTN study and received URD HCT at the participating centers during the time the trial was open but did not enroll in the study. Because not all information needed to determine eligibility for the protocol (organ function requirements) was available from the CIBMTR database, we selected patients treated with similar regimens to identify a group as close as possible in clinical profile to the trial participants. The assumption was that patients able to receive regimens used in the clinical trial were likely to have organ function consistent with eligibility criteria for the trial.

Study Outcomes

We estimated the proportion of all potentially eligible URD transplantations that were enrolled on the protocol. Survival, relapse, transplantation-related mortality (TRM), and occurrence of acute and chronic GVHD were compared between the participants and nonparticipants. *TRM* was defined as death while in complete remission. TRM and relapse were considered competing risks where occurrence of 1 of them prevents occurrence of the other. *Overall survival* (OS) was calculated as time from transplantation to death. Death from any cause was considered as an event and surviving patients were censored at the time of last follow-up. *Disease-free survival* (DFS) was defined as time from transplantation to treatment failure (death or relapse). Patients alive in remission were censored at the time of last follow-up.

Statistical Analysis

The characteristics of the participants and nonparticipants in the entire cohort and the separate PB and BM subgroups were compared using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Multivariate analyses of acute and chronic GVHD, TRM, relapse, DFS, and OS were performed using Cox proportional hazards regression, using participation in the BMT CTN study as the main effect. Variables considered in the multivariate analysis are described in Supplementary Table 2. The assumption of proportional hazards was tested for each variable using a time-dependent covariate and appropriate adjustments were performed where needed. Multivariate models were built using a forward-variable selection method. In addition, stratified analysis of BM and PB recipients was performed to compare the outcomes of BMT CTN 0201 participants versus nonparticipants within each graft source subgroup because the proportion of graft source was significantly different between the study participants and nonparticipants. All *P* values are 2 sided and a level of