Biol Blood Marrow Transplant 21 (2015) 113–118

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Abnormal Echocardiography 7 Days after Stem Cell Transplantation May Be an Early Indicator of Thrombotic Microangiopathy

Christopher E. Dandoy [1,*], Stella M. Davies [1], Russel Hirsch [2], Ranjit S. Chima [3], Zachary Paff [3], Michelle Cash [2], Thomas D. Ryan [2], Adam Lane [1], Javier El-Bietar [1], Kasiani C. Myers [1], Sonata Jodele [1]

[1] Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[2] Division of Cardiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
[3] Division of Critical Care Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Article history:
Received 20 May 2014
Accepted 24 September 2014

Key Words:
Pulmonary hypertension
Pericardial effusion
Left ventricle depression
Thrombotic microangiopathy
Echocardiography
Hematopoietic stem cell transplantation

A B S T R A C T

Cardiac complications after hematopoietic stem cell transplantation (HSCT) can lead to significant morbidity and mortality. Cardiac evaluation during the first 100 days after HSCT is usually performed only if clinically indicated, and no studies have examined whether routine screening is beneficial in this patient population at high risk for tissue injury. We conducted a single-center prospective clinical study to screen for cardiac complications in pediatric and young adult patients. One hundred consecutive HSCT patients underwent scheduled echocardiographic screening on day +7 after transplantation, independent of their clinical condition. At least 1 abnormality was identified in 30% of cases. Seventeen children had a pericardial effusion, 13 elevated right ventricular pressure, and 3 reduced left ventricular function. Survival was reduced in children with any echocardiographic abnormality at day 7 (67% versus 80% in those with and without, respectively, abnormality, $P = .073$). Moreover, raised right ventricular pressure at day +7 was significantly associated with transplant-associated thrombotic microangiopathy (TA-TMA; $P = .004$) and may indicate early vascular injury in the lungs. These data suggest that echocardiography 7 days after HSCT can detect early cardiac complications of HSCT and may identify early vascular injury associated with TA-TMA.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is an important and effective treatment strategy for many malignancies, marrow failure syndromes, and immunodeficiencies in children and young adults. The chemotherapy and radiation used in HSCT may cause significant cardiac and vascular endothelial toxicity, resulting in complications after transplant, such as pericardial effusion (PEF), left ventricular (LV) dysfunction, and pulmonary hypertension (PH). Moreover, heart disease is a major cause of long-term morbidity and mortality in survivors of HSCT in childhood [1].

Predicting the impact of cardiac complications in pediatric patients after HSCT is challenging because of the lack of prospective studies evaluating these factors. PEF, if left untreated, can cause cardiac tamponade, acutely decreasing cardiac function [2-6]. The reported incidence of PEF in retrospective cohorts has varied from 0.2% to 19% in patients after HSCT [7,8]. In our institution, we found a high incidence of PEFs in patients with transplant-associated thrombotic microangiopathy (TA-TMA) [9]. LV dysfunction has been reported in patients after high-dose cyclophosphamide and anthracyclines, and patients with LV dysfunction can initially be asymptomatic [10-12]. PH is associated with increased pulmonary vascular resistance and subsequent elevation in pulmonary artery pressures [13-15]. If undiagnosed, increased pulmonary artery pressure leads to elevated right ventricular (RV) pressure, cardiac failure, and death [14,16,17]. The initial symptoms of PH can be vague, and respiratory complications after HSCT are common, making the diagnosis of PH difficult [14,18]. Jodele et al. [19] reported a 2.3% incidence of PH with 80% mortality in a retrospective analysis of patients transplanted at our institution. All 5 patients who developed PH had histologic evidence of TMA in pulmonary arterioles, suggesting TA-TMA might be involved in pathogenesis of PH after HSCT.

Financial disclosure: See Acknowledgments on page 117.

* Correspondence and reprint requests: Christopher E. Dandoy, MD, Division of Bone Marrow Transplant and Immune Deficiency, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 11027, Cincinnati, OH 45229.
E-mail address: christopher.dandoy@cchmc.org (C.E. Dandoy).

http://dx.doi.org/10.1016/j.bbmt.2014.09.028
1083-8791/

We conducted a prospective single-institution study to determine the value of early post-transplant echocardiographic screening for PH, LV dysfunction, and PEF 7 days after HSCT in children and young adults. We hypothesized that scheduled post-transplant echocardiographic screening at day +7 would identify patients at risk for cardiac complications, leading to early clinical interventions and improved outcomes.

METHODS

In January 2012 we established uniform screening guidelines to monitor for acute cardiac complications after HSCT in pediatric and young adult patients at Cincinnati Children's Medical Center. All patients undergoing HSCT had echocardiographic evaluation within 30 days before starting their HSCT conditioning regimen (baseline echocardiography) and repeat echocardiography on day +7 independent of clinical condition. Patients with abnormal echocardiography on day +7 had follow-up echocardiography in 7- to 14-day intervals. Patients who were admitted to the pediatric intensive care unit (PICU) for cardiorespiratory failure or TA-TMA or had signs or symptoms of shock were additionally evaluated with echocardiography on arrival to the PICU. The pediatric cardiology service evaluated patients with PEF or LV dysfunction on echocardiography, whereas the PH service evaluated those with elevated RV pressures or other signs of PH.

The aim of this analysis was to determine the utility of the scheduled patient screening on day +7 after HSCT in detecting elevated RV pressure, PEF, and LV dysfunction and predicting adverse outcomes. Our secondary aim was to identify risk factors associated with the development of PEF, elevated RV pressure, and LV dysfunction.

Study Population

The study population consisted of 100 consecutive children and young adults who received HSCT at Cincinnati Children's Hospital Medical Center from January 2012 to March 2013. Data were collected prospectively after institutional review board approval. Data collected included patient demographics, echocardiography data, disease and therapy characteristics, transplant complications, and therapy outcomes. Currently accepted clinical criteria were used for diagnosis of acute graft-versus-host disease [20], veno-occlusive disease of the liver [21], viremias, and transplant-related mortality [22]. Respiratory failure was diagnosed in patients requiring endotracheal intubation and mechanical ventilation. One-year overall survival (OS) was counted from day 0 (stem cell infusion) to 1-year post-transplant or death. Finally, we evaluated oxygen requirement, respiratory failure, and hypertension during the first 100 days. Patients were categorized as having severe systemic hypertension if they required a continuous antihypertensive infusion and/or 3 or more antihypertensive medications to maintain systolic blood pressure below 95 percentile for age and height [23].

Diagnosis of TA-TMA

Patients were diagnosed with TA-TMA if the following laboratory criteria occurred concurrently and were documented on at least 2 tests: (1) elevated lactate dehydrogenase above the upper limit of normal, (2) new-onset thrombocytopenia less than 50×10^9/L or a greater than 50% decrease in the platelet count, (3) evidence of schistocytes in the peripheral blood, (4) new-onset anemia below the lower limit of normal, (5) negative Coombs test, and (6) the absence of coagulopathy. The date of TA-TMA diagnosis was defined as the first date when all diagnostic criteria were fulfilled [24-27].

Echocardiography Screening Protocol

Each HSCT patient received a comprehensive echocardiographic study at the time points listed above. Echocardiography screening included assessment of LV systolic function, PEF, and evaluation for PH. PH assessment was performed using the PH protocol as previously described [17].

A licensed technician performed all echocardiographic studies, and pediatric cardiologists reviewed all evaluations. A dedicated pediatric PH specialist reviewed abnormal PH-specific echocardiograms. Pulmonary artery pressure was estimated from a trans-tricuspid valve gradient calculated from the maximum velocity of continuous Doppler tricuspid regurgitation, using a modified Bernoulli equation and assuming right central venous pressure of 5 mm Hg [28,29]. PEF was identified from the separation of pericardial layers detected on echocardiography [4,6]. LV function was evaluated by assessment of the LV ejection fraction and/or shortening fraction [11].

Elevated RV pressure was defined as RV pressure greater than 35% of the patient's systolic blood pressure at time of echocardiography [17,28,30,31]. Intraventricular septal flattening was also evaluated in the determination of elevated RV pressure [32]. Echocardiography has a high sensitivity in predicting PH; however, the specificity is low until the estimated RV pressure approaches 50% systemic [29-31,33]. Therefore, patients who had a documented increase in RV pressures after HSCT to 35% to 49% of systemic were classified as "at risk for PH," and those with RV pressures of at least 50% of systemic were diagnosed with PH [17].

Patients were diagnosed with PEF if a new or enlarging PEF was found after transplant. PEFs were clinically classified as "small" (no interventions), "moderate to large" (medical interventions required), and "tamponade" (surgical intervention required) per standard guidelines [4]. Cardiac tamponade was diagnosed when echocardiography demonstrated diastolic collapse of the anterior RV free wall, right atrial collapse, left atrial, and/or LV collapse [5,34].

LV function was measured by ejection fraction, which represents the volumetric fraction of blood pumped out of the ventricle, and fractional shortening, an additional sensitive and specific measurement to assess LV function. Patients found to have an ejection fraction of 50% or less and/or a fractional shortening level less than 2 standard deviations below the age-adjusted mean [11] were determined to have LV dysfunction. Patients were identified as having an abnormal echocardiogram at day +7 if they were found to have at least 1 of the above-mentioned outcome measures: elevated RV pressure, PEF, and/or LV dysfunction.

Statistical Analysis

Descriptive statistics were reported as medians, interquartile ranges, and frequencies. Differences in categorical and continuous variables were assessed with the Fisher exact and Wilcoxon rank sum tests, respectively. Associated odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method. Multivariate analysis was performed to evaluate associations between abnormal echocardiography findings at day +7 and patient age, underlying disease, conditioning regiment, graft-versus-host disease prophylaxis, and autologous versus allogeneic HSCT. The sensitivity, specificity, and positive and negative predictive values of elevated RV pressure and/or PEF at day +7 at diagnosing TA-TMA was estimated.

One-year OS comparing patients with abnormal echocardiography with those without was calculated with Kaplan-Meier analysis with the associated *P* values calculated by log-rank analysis. Cumulative incidence of TA-TMA with death as a competing variable was calculated by Gray's method [35]. All patients were diagnosed with TA-TMA before 100 days post-HSCT, so relapse was not considered as a competing risk for TA-TMA because all patients relapsed after this time.

All statistical test conducted were 2-sided, and $P < .05$ was considered significant. Cumulative incidence was calculated in R [36,37]. All other data analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL).

RESULTS

Patient Demographics

We analyzed echocardiographic screening data from 100 consecutive HSCT patients; demographics of this patient population are shown in Table 1. Most study patients were white, with a median age of 5.4 years. Sixty-two percent received transplantation for nonmalignant disorders, mainly primary immune deficiencies (36%) and bone marrow failure syndromes (21%). Eighty-four percent of patients underwent allogeneic HSCT, and 86% of the allogeneic grafts were from unrelated donors. Bone marrow was the most common stem cell source, used in 59% of patients. Peripheral blood stem cells were used mainly for autologous stem cell transplantation (n = 16) and patients with Fanconi anemia as an ex vivo T cell–depleted graft (n = 11). Cord blood was used when a suitable bone marrow donor was not available. The conditioning regimen was myeloablative in 42% and reduced intensity in 58% of patients; 9% of patients received total body radiation.

OS of Patients with Abnormal Echocardiography at Day +7

Thirty of 100 screened patients (30%) had abnormal echocardiography at day +7 (Figure 1). Most patients with abnormal echocardiography were asymptomatic, and abnormal echocardiography was not associated with fluid retention. Thirteen patients had elevated RV pressure