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Significant Transplantation-Related Mortality from Respiratory Virus Infections within the First One Hundred Days in Children after Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Respiratory viral infections (RVI) are important in hematopoietic stem cell transplantations (HSCT) and knowledge regarding incidence, morbidity, mortality, and long-term pulmonary complications is limited. We report a study to evaluate incidence and outcomes, both short and long-term, of RVI in children receiving HSCT. Between January 2000 and December 2012, 844 patients underwent hematopoietic stem cell transplantation (HSCT) at the Hospital for Sick Children: 491 were allogeneic and 353 were autologous. When screening for causes of death in the first year after HSCT in the 844 patients, we found that RVI as a cause of death was only evident in the first 100 days after HSCT. Fifty-four (6.5%) patients were found to have an RVI within the first 100 days after HSCT (allogeneic = 32, autologous = 22). Upper and lower respiratory tract infections were documented in 31 (57%) and 23 (43%) patients, respectively. Viruses were parainfluenza (35%), respiratory syncytial virus (28%), influenza (22%), adenovirus (7%), human metapneumovirus (4%), coronavirus (2%), and rhinovirus (2%). Three patients relapsed with their primary disease before day 100 and were excluded. The overall mortality for the remaining 51 patients was 10% (allogeneic = 4, autologous = 1). All 5 deaths were directly attributable to RVI and all 5 deaths occurred in patients with a lower respiratory tract infection. The remaining patients were followed for a median of 4.3 years (range, 1.4 to 11.8) and no chronic pulmonary complications were observed. A clear seasonal pattern for contracting RVI was evident with 65% of total RVI occurring between October and March (35 of 427 versus 19 of 417, $P = .03$). Given the significant mortality from RVI and the challenges in preventing them, choosing the time to start HSCT, whenever possible, may help prevent RVI and improve outcomes.

INTRODUCTION

Infections are 1 of the main complications after hematopoietic cell transplantation (HSCT) and respiratory viral infections (RVI) are being increasingly recognized as important complications after HSCT with variable degrees of morbidity and mortality [1-4]. In recent years, the growing number of HSCT utilizing alternative donors and cord progenitor stem cells, along with the common use of serotherapy, has contributed to a significant increase in viral infections after HSCT [5,6]. Some well-known viruses, such herpes simplex virus (HSV) and cytomegalovirus (CMV), were major causes of morbidity and mortality in HSCT [7,8]. However, since prophylactic or preemptive anti-HSV/CMV therapy became standard practice, morbidity and mortality from HSV or CMV disease are rare [9,10]. Nonetheless, respiratory viruses such as influenza, parainfluenza, and respiratory syncytial virus (RSV) continue to be a major cause of morbidity and mortality in patients after HSCT and there is increased awareness for the diagnosis of these infections. However, no prophylactic approach for such viruses exists in HSCT recipients. Hence, this study's aim was to investigate the incidence and risk factors of RVI in children after HSCT and describe the short- and long-term outcomes of these patients.

PATIENTS AND METHODS

This study was approved by our institutional research ethics board. The medical records of children who received HSCT from January 2000 to

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December 2012 at the Hospital for Sick Children, Toronto were reviewed to identify those patients who had a positive test for respiratory virus obtained by nasopharyngeal aspirate (NPA), bronchoalveolar lavage (BAL), pleural tap, or lung biopsy specimen. Microbiological testing included the following methodologies: (1) virus isolation in cell culture (2000 to 2007 for NPA and 2000 to 2011 for BAL and biopsies) for influenza A and B, RSV, parainfluenza virus 1 through 3, and adenovirus; (2) direct fluorescent antibody testing (2000 to 2012) on all NPAs, bronchoscopic BALs for 8 viruses (influenza A and B, RSV, parainfluenza virus 1 through 3, adenovirus, and human metapneumovirus (hMPV); (3) PCR for the pandemic influenza strain (May to December 2009); (4) PCR for adenovirus (2002 to 2012); and (5) multiplex PCR (May 2011 to December 2012) for influenza A and B, RSV, parainfluenza virus 1 through 4, adenovirus, hMPV, enterovirus, rhinovirus, bocavirus, and coronaviruses. Data collected included patient demographics, indication for HSCT, type of transplantation (allogeneic or autologous), graft type, conditioning regimen, donor details for allogeneic patients, graft-versus-host disease (GVHD) prophylaxis, time from HSCT to positive respiratory virus result, clinical course, transplantation-related mortality (TRM) and cause, long-term pulmonary complications, and overall survival.

Definitions

The following definitions were used in the study. An *upper respiratory tract infection* (URTI) was defined as detection of an RVI from upper respiratory secretions together with symptoms from the upper respiratory tract (nose and throat). A *lower respiratory tract infection* (LRTI) was defined as either hypoxia or pulmonary infiltrates together with identification of an RVI in upper respiratory secretion, BAL, pleural tap, or lung biopsy. The *day of engraftment* was defined as the first of 3 consecutive days in which the peripheral absolute neutrophil count was $> .5 \times 10^9$/L. *TRM* was defined as being either due to an RVI or other transplantation toxicities. *Death due to RVI* was defined as death from respiratory failure with no other cause of the pneumonia. *Long-term pulmonary complication* was defined as any limitation of pulmonary status, including pulmonary function tests. *Relapse* was defined by the finding of hematologic or cytogenetic recurrence or by the initiation of therapy for recurrence. *Progressive disease* was defined as tumor growth of more than 20% or spreading since undergoing transplantation [11].

Supportive Care

All patients were nursed in protective isolation in single rooms with high-efficiency particulate air filters. All patients had indwelling central venous catheters and the majority received nutritional support with nasogastric feeding or total parenteral nutrition. Infection prophylaxis included fluconazole for fungal prophylaxis, ganciclovir for CMV prophylaxis (2000 to 2005), and preemptive strategy from 2005 onwards. Growth factors were given as indicated, and laminar air flow rooms were used from day 0 until engraftment. Intravenous immunoglobulin at a dose of .5 g/kg was supplemented if the IgG level was less than 400 mg/dL. The IgG level was routinely monitored every week in all patients. *Pneumocystis jiroveci* prophylaxis was given before HSCT and after HSCT for at least 6 months. Pneumococcal prophylaxis with penicillin continued for at least 1 year or until the administration of pneumococcal vaccine. Blood products were transfused to maintain hemoglobin concentration > 70 mg/L and platelet counts of 20,000/mm^3. Fever during the neutropenic phase was treated with broad-spectrum antibiotics and amphotericin or caspofungin, as necessary, and modified subsequently according to the results of blood or tissue cultures.

Clinical Follow-Up

Patients received their preparatory regimen, underwent transplantation, and recovered in the hospital, where they were examined by the medical team twice each day until they achieved engraftment. All patients with respiratory symptoms were investigated for the presence of respiratory viruses. Chest radiographs and computed tomography scans were obtained if clinically indicated. NPAs, throat swaps, or nasal swabs were used for obtaining upper respiratory specimens. BAL or pleural tap and/or lung biopsy were used for obtaining lower respiratory specimens.

Endpoints

The primary endpoint of the study was to review all RVI-positive patients after HSCT and describe their outcome in terms of TRM and long-term pulmonary complications.

Statistics

Univariate logistic regression models were constructed to analyze the impact of risk factors on TRM within the first 100 days, including transplantation type (allogeneic versus autologous), graft type (bone marrow versus peripheral blood stem cells versus cord blood), utilization of serotherapy (antithymocyte globulin, Alemtuzumab [MabCampath; Genzyme Canada Inc., Mississauga, Ontario], and no serotherapy), and underlying disorder (malignant versus benign). All reported *P* values were 2-sided, and a significance level of .05 was used. All statistical analyses were carried out using SPSS version 12.5.

RESULTS

Eight hundred forty-four patients underwent HSCT at the Hospital for Sick Children, Toronto, Canada during the study period and comprise the study population. The transplant recipients consisted of 341 female and 503 male patients, with a median age of 7.5 years (range, 1 month to 17.8 years). The HSCT was allogeneic in 491 patients and autologous in 353 patients. The diseases for which HSCT was performed were acute lymphoblastic leukemia (n = 138), acute myeloid leukemia (n = 110), myelodysplastic syndrome (n = 21), severe aplastic anemia (n = 49), inherited marrow failure (n = 29), primary immune deficiency (n = 58), non-Hodgkin lymphoma (n = 44), Hodgkin disease (n = 28), chronic myelogenous leukemia (n = 16), metabolic diseases (n = 25), hemophagocytic lymphohistiocytosis (n = 17), brain tumors (n = 103), solid tumors (n = 179), thalassemia (n = 15), and others (n = 12).

Incidence of RVI

During the study period and among the 844 HSCT recipients, 96 patients with RVI were documented. Screening for causes of death in the 96 patients, we found that RVI was never the cause of death after day 100 after HSCT. In the first 100 days after HSCT, there were 54 patients with RVI. As these 54 patients were the focus of the study, their diagnosis and conditioning regimen including use of serotherapy are described in Table 1. Only 1 patient with diagnosis of severe combined immune deficiency (SCID)/Omenn's syndrome received conditioning with busulfan and cyclophosphamide. The remaining 5 SCID patients did not receive any conditioning regimen. When analyzing utilization of serotherapy, we found 11 patients who received antithymocyte globulin and 1 who received alemtuzumab.

The overall frequency of documented RVI in the first 100 days after HSCT was 6.4%. The frequency was slightly higher in allogeneic (6.5%) than in autologous (6.2%) transplantations ($P = .867$). Twenty-three patients had LRTI: 17 occurring in allogeneic patients and 6 in autologous HSCT patients. The frequency of a LRTI was 3.5% in allogeneic and 1.7% in autologous HSCT patients. Nineteen patients had parainfluenza infections (11 allogeneic, 8 autologous). Six patients had LRTI and 13 patients had URTI. The median time to diagnosis of parainfluenza infection was 25 days (range, 1 to 81 days) after HSCT. One patient with LRTI was treated was with ribavirin. Fifteen patients had RSV infection (9 allogeneic, 6 autologous). Eight had LRTI and 7 had URTI. The median time to diagnosis of RSV infection was 14 days (range, 1 to 52 days) after HSCT. Six patients with LRTI were treated with ribavirin immediately after RSV was identified. Health Canada approved palivizumab (RSV Ig) in 2012 and only 1 patient received it. Twelve patients had influenza infection (7 allogeneic, 5 autologous). Eight patients had influenza A and 4 had influenza B. Four patients had LRTI and 8 patients had URTI. The median time to diagnosis of influenza infection was 31 days (range, 1 to 100 days) after HSCT. All 12 patients received oseltamivir. Four patients had adenovirus infections (3 allogeneic, 1 autologous) proven by adenovirus PCR positive from BAL or pleural fluid and/or lung biopsy. All of them had LRTI and subsequently developed respiratory distress. The median