CLINICAL RESEARCH

Cord-Blood Hematopoietic Stem Cell Transplant Confers an Increased Risk for Human Herpesvirus-6-Associated Acute Limbic Encephalitis: A Cohort Analysis

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Human herpesvirus-6 (HHV-6) frequently reactivates after allogeneic hematopoietic stem cell transplantation (HSCT); its most severe manifestation is the syndrome of posttransplantation acute limbic encephalitis (HHV-6-PALE). The epidemiology, risk factors, and characteristics of HHV-6-PALE after unrelated cord-blood transplantation (UCBT) are not well characterized. We analyzed 1344 patients undergoing allogeneic HSCT between March 2003 and March 2010 to identify risk factors and characteristics of HHV-6-PALE. The cohort included 1243 adult-donor HSCT and 101 UCBT recipients. All patients diagnosed with HHV-6-PALE had HHV-6 DNA in cerebrospinal fluid (CSF) specimens in addition to symptoms and studies indicating limbic encephalitis. Nineteen cases (1.4%) of HHV-6-PALE were identified during this study: 10 after UCBT (9.9%) and 9 after adult-donor HSCT (0.7%), for an incidence rate of 1.2 cases/1000 patient-days compared to 0.08 cases/1000 patient-days ($P < .001$), respectively. Risk factors for HHV-6-PALE on multivariable Cox modeling were UCBT (adjusted hazard ratio [aHR], 20.0; 95% confidence interval [CI], 7.3-55.0; $P < .001$), time-dependent acute graft-versus-host disease (aGVHD) grades II to IV (aHR, 7.5; 95% CI, 2.8-19.8; $P < .001$), and adult-mismatched donor (aHR, 4.3; 95% CI, 1.1-17.3; $P = .04$). Death from HHV-6-PALE occurred in 50% of affected patients undergoing UCBT and no recipients of adult-donor cells. Patients receiving UCBT have increased risk for HHV-6-PALE and greater morbidity from this disease.

Biol Blood Marrow Transplant 18: 1638-1648 (2012) © 2012 American Society for Blood and Marrow Transplantation

KEY WORDS: Herpes, HHV-6, Transplantation, Cord, Encephalitis

INTRODUCTION

Human herpesvirus-6 (HHV-6) is an opportunistic pathogen in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Primary infection with this herpesvirus typically occurs during infancy [1]. After acute infection, HHV-6 is able to establish latency in a wide variety of host cells, although it replicates most efficiently in vitro in $CD4^+$ T lymphocytes [2]. There are 2 closely related variants of HHV-6, types A and B; HHV-6B is the more frequent cause of human disease. Antibodies to either or both variants are found in >95% of adults [2-5]. HHV-6 DNA becomes detectable in plasma samples from approximately 40% to 50% of patients undergoing HSCT from adult donors and up to 80% of patients after unrelated umbilical cord blood HSCT (UCBT) within 6 weeks after transplantation, a phenomenon attributed most commonly to HHV-6 reactivation [6-11]. The HHV-6B variant accounts for approximately 98% of these events [12-14]. HHV-6 reactivation after HSCT has been associated with many complications including delayed engraftment, graft rejection, grade II to IV acute graft-versus-host disease (aGVHD), central nervous system (CNS) disease, and increased all-cause mortality [9,11,15-24].

One of the most debilitating and sometimes fatal consequences of HHV-6 reactivation after HSCT is the syndrome of posttransplantation acute limbic

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Presented in abstract form at the 53rd Annual Meeting of the American Society of Hematology, San Diego, CA. 2011: Abstract 649.

Financial disclosure: See Acknowledgment on page 1647.

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Received March 26, 2012; accepted April 30, 2012

1083-8791/$36.00
doi:10.1016/j.bbmt.2012.04.016

encephalitis (HHV-6-PALE) [9,19-24]. Risk factors for this disease are poorly understood and variably reported as younger age, mismatched or unrelated donor (URD), sex mismatched donor, underlying malignancy other than hematologic malignancy in first remission or chronic myelogenous leukemia chronic phase, low pre transplantation anti-HHV-6 IgG titer, treatment with anti-T cell monoclonal antibodies or steroids, high-level plasma HHV-6 viremia, and aGVHD grades II to IV [7-10,15,23,25-27].

HHV-6-PALE after HSCT is well described [9,19-24]. Several case reports and series of HHV-6-PALE after UCBT have been published [21,28-30], but the epidemiology, risk factors, and characteristics of this syndrome in patients receiving UCBT are not well characterized. Given the increased incidence of HHV-6 reactivation and higher plasma viral loads in recipients of UCB [6,7], these patients may be at risk for more frequent and severe manifestations of CNS disease. This study describes the epidemiology, risk factors, and characteristics of HHV-6-PALE in patients undergoing UCBT at our institution.

PATIENTS AND METHODS

Patients

All patients who underwent an initial allogeneic HSCT between March 2003 and March 2010 were identified through the clinical database at Dana-Farber Cancer Institute/Brigham and Women's Hospital (DFCI/BWH) Hematopoietic Stem Cell Transplantation Program. This period was chosen to correspond with the introduction of UCBT at our institution and the availability of a standardized HHV-6 cerebrospinal fluid (CSF) PCR assay for testing all samples at a single reference laboratory. A waiver of the requirement for informed consent was granted by the Office for Human Research Studies of Dana-Farber/Harvard Cancer Center.

A total of 1367 patients underwent allogeneic HSCT during the study period. Twenty-three patients were excluded due to receiving an initial allogeneic HSCT before the start of the study period or during the study period at an outside institution. A final cohort of 1344 patients undergoing initial allogeneic HSCT during the study period was used for this analysis: 725 were from adult URDs (633 HLA-matched at 6/6 loci, 92 HLA-mismatched), 518 from adult related donors (508 HLA-matched, 10 HLA-mismatched), and 101 from mismatched UCB donors (Tables 1 and 2). Fifteen patients underwent a second HSCT procedure during the 100-day follow-up period from the date of the initial HSCT. In this group, 8 patients had 2 UCBTs, 6 patients had 2 HSCTs from adult donors, and 1 patient had an adult-donor HSCT followed by UCBT. Neither foscarnet nor ganciclovir were used for antiviral prophylaxis during this study period. Patients received preemptive therapy for cytomegalovirus (CMV) DNAemia primarily with ganciclovir or valganciclovir, based on a CMV hybrid capture assay (Digene, Gaithersburg, MD) or a real-time PCR assay (Qiagen, Germantown, MD).

Covariates and Definitions

Data on covariates of interest (Tables 1 and 2) were identified through the DFCI/BWH HSCT database, the Partners Healthcare System Research Patient Data Repository, and review of the electronic and paper medical records. Engraftment day was defined as the first of 3 consecutive days of an absolute neutrophil count greater than >500 cells/μL. Incidents of aGVHD were defined according to the consensus criteria [31], and data were collected for day of onset, maximum overall grade, and drugs used for treatment.

Conditioning regimens were grouped as myeloablative or reduced-intensity conditioning (RIC). Myeloablative conditioning consisted of different combinations of chemotherapeutic agents, but a majority included cyclophosphamide and 1400 cGy total body irradiation (TBI) delivered in 7 fractions [32]. A minority received high-dose busulfan and cyclophosphamide. RIC primarily consisted of fludarabine with low-dose busulfan or fludarabine with melphalan, combined with rabbit anti-thymocyte globulin (ATG; at a dose of 6 mg per kilogram of body weight) [33]. ATG use was primarily restricted to RIC UCBT and a few cases of RIC adult-donor HSCT [34,35]. Prophylaxis for GVHD in patients undergoing adult-donor HSCT consisted of tacrolimus with methotrexate and/or sirolimus in a majority of cases, as well as cyclosporine with mycophenolate mofetil [32]. In UCBT, GVHD prophylaxis consisted primarily of tacrolimus with sirolimus or cyclosporine with mycophenolate mofetil [34-36]. Patients participated in single-arm or randomized protocols or were treated with conditioning and aGVHD prophylaxis regimens at the discretion of the treating physicians.

HHV-6-PALE was diagnosed in patients who had detectable HHV-6 DNA in their CSF in the context of acute-onset altered mental status, amnesia, seizures, or other evidence of medial temporal lobe disease involving the limbic system and no other identifiable etiology after extensive workup [19]. Cases were reviewed in detail for day of HHV-6-PALE symptom onset, CSF results, electroencephalogram (EEG) and magnetic resonance imaging (MRI) findings, antiviral and anticonvulsant treatments, concomitant clinical and laboratory findings, and patient outcomes.

HHV-6 Testing

Prospective and routine monitoring of plasma HHV-6 DNA by PCR after HSCT was not performed in this patient cohort. Testing was performed at the