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HHV-6 Reactivation and Associated Sequelae after Hematopoietic Cell Transplantation

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Human herpesvirus 6 (HHV-6) reactivation has been associated with acute graft-versus-host-disease (aGVHD), cytomegalovirus reactivation, and mortality after allogeneic hematopoietic cell transplantation (HCT), but previous studies have yielded inconsistent results. We performed a large prospective study of allogeneic HCT recipients in order to more definitively define the relationships between HHV-6 and these important outcomes. Plasma specimens were collected prospectively from 315 allogeneic HCT recipients and tested for HHV-6 DNA at baseline and twice weekly for 12 weeks. Cox proportional hazards models were used to evaluate the time-dependent associations between HHV-6 reactivation and the targeted outcomes. HHV-6 was detected in 111 of 315 patients (35%) at a median of 20 days after HCT. HHV-6 reactivation was associated with subsequent cytomegalovirus reactivation (adjusted hazard ratio [aHR], 1.9; 95% confidence interval [CI], 1.3-2.8; $P = .002$). High-level HHV-6 (>1,000 HHV-6 DNA copies/mL) was associated with subsequent grades II to IV aGVHD (aHR, 2.4; 95% CI, 1.60-3.6; $P < .001$). High-level HHV-6 reactivation was also associated with nonrelapse mortality (aHR, 2.7; 95% CI, 1.2-6.3; $P = .02$). HHV-6 reactivation was independently and quantitatively associated with increased risk of subsequent cytomegalovirus reactivation, aGVHD, and mortality after HCT. A randomized antiviral trial is warranted to establish causality between HHV-6 and these endpoints and to determine if reducing HHV-6 reactivation will improve outcome after HCT.

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INTRODUCTION

Human herpesvirus 6 (HHV-6) infects 90% to 100% of individuals during early childhood [1]. After primary infection, HHV-6 establishes a latent infection in hematopoietic reservoirs. This latent infection can become active in settings of severe immunosuppression, especially hematopoietic cell transplantation (HCT). Prior studies show that HHV-6 reactivates in approximately 40% of patients after HCT [2-4], and reactivation has variably been associated with important outcomes, including cytomegalovirus (CMV) reactivation [5], acute graft-versus-host-disease (aGVHD) [2,6,7], and increased mortality [4,6]. Whether HHV-6 is actually causally associated with these problems remains controversial.

We performed a large prospective study of HHV-6 in HCT recipients in an effort to better understand the relationships between HHV-6, CMV, aGVHD, and mortality in these patients.

MATERIALS AND METHODS

The data presented in this report were generated in part from a prospective study designed to evaluate the associations between HHV-6 reactivation and neuropsychiatric and neurocognitive outcomes [8]. The protocol was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Patients

Patients of all ages undergoing allogeneic HCT from January 2005 through August 2008 were eligible for enrollment. Those with limited English proficiency were excluded due to the frequent neuropsychiatric and neurocognitive assessments required for the

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parent study. The study was presented to 880 patients during the pretransplantation evaluation, and 474 were preliminarily enrolled (Figure 1). Of the 474 patients, a total of 152 withdrew or were deemed ineligible before contributing data, leaving 322 patients who contributed data. Six patients with HHV-6 DNA levels suggestive of chromosomal integration [9] (determined a priori as increasing HHV-6 plasma DNA levels during the first 2 weeks after HCT and persistent levels ≥100 copies per/mL in ≥80% of subsequent plasma samples) were excluded from analyses. An additional patient, who contributed only baseline data, was also excluded. Of the 315 included patients, nearly all (n = 308; 98%) were followed for ≥4 weeks after HCT or until death.

Clinical Care

Participation in this study had no impact on clinical decisions, including those involving conditioning regimens, type of transplantation, aGVHD prophylaxis and treatment, or administration of antimicrobials. There were no recipients of T cell-depleted stem cell grafts. CMV reactivation was monitored and treated per clinical standards of care. From the initiation of the study through February 2007, the primary mode of CMV screening was CMV antigenemia. After this point, plasma CMV PCR became the primary means of CMV screening. Patients were tested weekly for evidence of CMV reactivation through approximately day 100 after HCT. A pre-emptive antiviral therapy approach was followed [10,11]. Ganciclovir was the first-line antiviral postengraftment, and foscarnet was the second.

Study Procedures

Baseline (pre-HCT) and twice-weekly plasma specimens were collected through day 84 post-HCT for HHV-6 testing. A total of 6,255 specimens were obtained (85% of planned). Patients were followed through day 200 for mortality.

Clinical Data and Definitions

Demographic, clinical, and laboratory information was collected from clinical records and databases.

Underlying disease was categorized as "less advanced" or "more advanced" (Table 1) [12].

Medical comorbidity was defined and categorized using a validated scale [13].

Pretransplantation lymphopenia was assessed at the last lymphocyte count obtained before starting conditioning chemotherapy and was defined as a lymphocyte count <600 (approximate lowest quartile).

Conditioning regimens were categorized as "myeloablative," "nonmyeloablative," or "reduced intensity." A variety of cytoreductive regimens were used; the most common regimens are reported in Table 1 by myeloablative category.

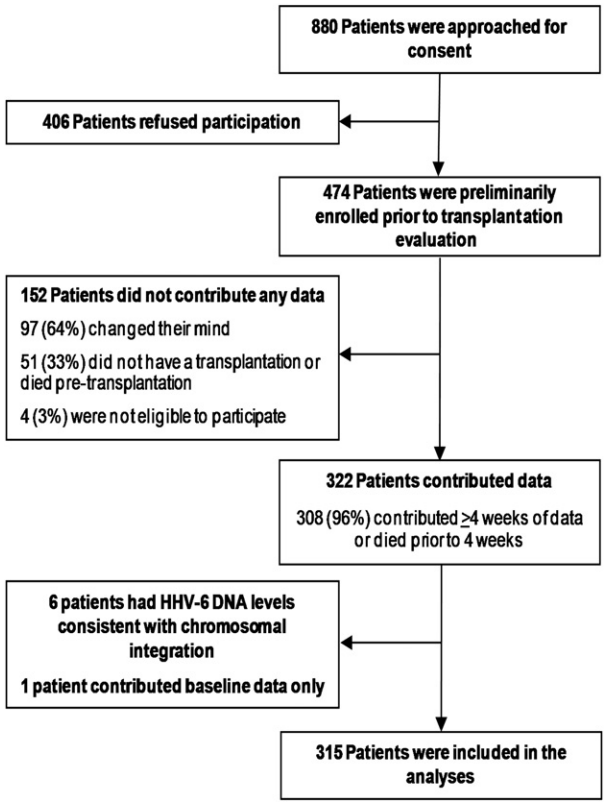

Figure 1. Consort diagram.

HHV-6 reactivation was defined as any level of plasma HHV-6 DNA.

High-level HHV-6 reactivation was defined as ≥1,000 HHV-6 DNA copies/mL plasma. This level was chosen because it is a threshold for CMV that is commonly used to initiate use of pre-emptive antiviral therapy. In addition, in the context of this study, it is close to the median maximum level (873 HHV-6 copies/mL plasma).

CMV reactivation was defined as any level of plasma CMV DNA or whole blood antigenemia.

High-level CMV reactivation was defined as ≥1,000 CMV DNA copies/mL plasma or 10 cells/high-powered field of CMV antigenemia.

Acute graft-versus-host disease (aGVHD) grades and organ-specific types (skin, gastrointestinal, and liver) and stages were categorized as previously described by a single investigator (P.J.M.) blinded to HHV-6 study results [14].

Chronic graft-versus-host disease (cGVHD) was categorized as previously described [15].

Overall mortality was defined as mortality occurring for any reason.

Nonrelapse mortality was defined as mortality occurring for reasons other than relapse in patients receiving myeloablative HCT or for reasons other than relapse or progression of underlying disease in patients receiving nonmyeloablative HCT.