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Herpes Zoster in Autologous Hematopoietic Cell Transplant Recipients in the Era of Acyclovir or Valacyclovir Prophylaxis and Novel Treatment and Maintenance Therapies

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The epidemiology of herpes zoster (HZ) in contemporary autologous hematopoietic cell transplant (HCT) recipients, and the impact of acyclovir (ACV)/valacyclovir (VACV) prophylaxis, is not well described. In this observational study from 2002 to 2010, we retrospectively identified 1000 varicella zoster virus (VZV)–seropositive autologous HCT recipients with up to 5 years of follow-up. The incidence of HZ and use of ACV/VACV prophylaxis were determined through review of medical records and mailed questionnaires. Risk factors for HZ were determined by multivariable Cox regression. Over a period of 5 years after autologous HCT, 194 patients developed at least 1 HZ episode, with a cumulative incidence of 21%; 159 of 194 (82%) were not on prophylaxis at the time of HZ. A second episode of HZ occurred in 31 of 194 (16%) patients. Patients taking ACV/VACV had reduced risk for HZ (adjusted hazard ratio [aHR], .59; 95% confidence interval [CI], .37 to .91), whereas those older than the median age (≥55.5 years) had increased risk (aHR, 1.42; 95% CI, 1.05 to 1.9). Disseminated VZV was reported in 8% and postherpetic neuralgia in 13% of patients. We demonstrate a high burden of HZ late after autologous HCT, despite long-term antiviral prophylaxis. Improved prevention strategies are needed to provide sustained protection against HZ after autologous HCT.

INTRODUCTION

Autologous hematopoietic cell transplantation (HCT) is a favored treatment option for many hematologic malignancies. The increasing use of novel chemotherapeutic regimens, T cell–depleting agents (eg, CD34 selection, ATG) and biologics, and maintenance therapies, along with an aging HCT population, poses a heightened risk for infections in this patient population [1-5]. Studies have reported herpes zoster (HZ) as a common infectious complication after autologous HCT in 16% to 30% of patients, with most events occurring in the first year after HCT [6-8].

In addition to the typical presentation of HZ with a painful dermatomal rash, HCT recipients often experience complications such as postherpetic neuralgia, ocular disease, and potentially fatal disseminated disease in one-third or more of affected patients [5,9-14]. Given the significant advances in the treatment and supportive care for autologous HCT recipients over the past decade, including the increased use of novel drugs for maintenance therapy after HCT (eg, bortezomib, lenalidomide) [1,2], a contemporary understanding of the long-term risk of HZ in this population is important.

Long-term varicella zoster virus (VZV) prophylaxis with acyclovir (ACV)/valacyclovir (VACV) has been shown to be safe and effective in allogeneic HCT recipients [9,14-17]. There is also evidence to support the utility of prolonged antiviral

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prophylaxis for up to 2 years after autologous HCT [18]. The 2009 international guidelines recommend ACV/VACV prophylaxis among VZV-seropositive patients for 1 year after allogeneic (B1 recommendation) and autologous (CII recommendation) HCT recipients [19]. The guidelines have a lower evidence rating in the setting of autologous HCT because of a limited number of studies [19], and consequently, the duration of prophylaxis ranges widely between HCT centers [20]. Although the number of autologous HCTs exceeds that of allogeneic HCTs [21], there is a relative lack of contemporary data regarding the epidemiology of HZ after autologous HCT and the impact of VZV prophylaxis in this population. Recent findings of substantially increased health care costs and utilization among cancer and HCT patients with HZ lends additional support to the need for such data [22].

The purpose of this study was to determine the incidence of and risk factors for HZ over a 5-year period after autologous HCT in a large retrospective cohort of patients who were prescribed long-term ACV/VACV for VZV prophylaxis.

MATERIALS AND METHODS

Data Collection

Databases and available medical records were retrospectively reviewed for patient demographics and clinical characteristics, including details regarding HZ episodes and use of antiviral prophylaxis. In addition to patient follow-up at our center, the Fred Hutchinson Cancer Research Center (FHCRC) long-term follow-up program prospectively sent post-HCT survey questionnaires to providers and patients followed outside of our center at 6 months after HCT and then annually. Physician medical records were also requested. The patient survey includes a question asking whether the patient had "…chicken pox or a Herpes zoster or Varicella zoster (VZV) infection (shingles)" and the area of the body involved since the prior questionnaire, as well as a section to list or select active medications. The physician survey includes a checkbox to indicate the diagnosis of "HZ/Shingles" since the last follow-up along with sections to document other medical complications. The survey did not inquire about microbiologic testing. Data obtained from medical records were given preference, followed by physician and then patient questionnaires. Report of HZ in any record was counted as an event in this study.

Herpes zoster, the primary endpoint, was classified as *localized*, defined as the presence of lesions distributed in 1 or 2 contiguous dermatomes or as *disseminated*, with lesions involving more than 2 dermatomes or any visceral or central nervous system involvement. Ocular involvement was classified as local disease for the purposes of this study. Diagnosis was at the discretion of the treating providers and may not have included microbiologic confirmation, as HZ is often a clinical diagnosis without additional microbiologic testing. Start and stop dates were collected from available records. If no clear date was indicated for the start of a HZ episode, the midpoint from date of last contact without notation of an event and date of first notation of the event was used. If the event was only indicated in physician or patient questionnaires, the midpoint from the dates covered by the questionnaires was used in the absence of additional data. Antiviral prophylaxis and maintenance therapy start and stop dates were abstracted using the same approach.

Patients

The study population included 1000 consecutive patients who underwent autologous HCT at FHCRC between November 2002 and December 2010, including tandem autologous-autologous HCT recipients receiving transplants within 6 months (Figure S1). Patients were excluded if they received a planned tandem autologous-allogeneic HCT, were VZV seronegative, received a VZV vaccine without prior HZ, or died within 30 days of HCT. Patients undergoing HCT for autoimmune diseases received regimens including CD34 selection and/or rabbit ATG in addition to conditioning with total body irradiation or high-dose chemotherapy.

Antiviral prophylaxis with ACV 800 mg by mouth twice daily or VACV 500 mg by mouth twice daily for 1 year after autologous HCT was routinely prescribed in this cohort per FHCRC guidelines. Most post-HCT maintenance therapy protocols, especially those using steroids or bortezomib, recommended continuation of ACV/VACV for 2 months beyond completion of maintenance therapy.

The FHCRC institutional review board approved the study. Informed consent was signed by all participating patients in accordance with the Declaration of Helsinki.

Statistical Analysis

The incidence rates of first HZ episode per person years and 1000 person days after first autologous HCT were calculated, accounting for date of death or last date of patient contact recorded in our system. Cumulative incidence curves were used to estimate the probability of developing an initial or recurrent episode of HZ, with death treated as a competing risk. The effect of ACV/VACV prophylaxis on the occurrence of first HZ episodes was evaluated in Cox regression models including demographic, HCT, and clinical characteristics. Univariable analysis for risk factors associated with a recurrent HZ episode was also performed, but limited events precluded an adjusted analysis. ACV/VACV prophylaxis and maintenance therapy were analyzed as time-dependent variables. Absolute lymphocyte count (ALC) thresholds above and below the lower quartile (760 cells/μL) were used because of limited events at lower thresholds.

Variables with biological relevance or P value ≤ .20 in univariable analyses were considered for multivariable analyses. Statistical significance was defined as 2-sided $P < .05$. SAS version 9.3 (SAS Institute, Cary, NC) was used for analyses.

RESULTS

Incidence of HZ

We retrospectively identified 1000 consecutive VZV seropositive patients receiving an autologous HCT at our center from 2002 to 2010. Patient demographic and clinical characteristics are presented in Table 1. Patients were followed for a median of 39.7 months (interquartile range [IQR], 20.7 to 66.1 months) and a total of 3778.1 person years. There were 359 deaths in this cohort during the study period at a median of 16.1 months (IQR, 7.3 to 37.9). Patients with 5 years of possible follow-up had return of questionnaires or records for a median of 4 out of 5 years, suggesting good data capture for events spanning the follow-up period. Additionally, patients on maintenance therapy or recurrent disease often returned or communicated with our center for continued follow up.

One hundred ninety-four patients developed at least 1 HZ episode after autologous HCT with an overall cumulative incidence of 21% (95% confidence interval [CI], 18% to 24%; Figure 1A). First HZ episodes occurred at a median of 19 months (IQR, 14.4 to 30.7; Table 2) after autologous HCT. Recurrence of HZ occurred in 31 of these patients (16%) at a median of 14.5 months after the first post-HCT HZ episode (IQR, 7.0 to 24.5; Table 2, Figure 1B). Time to HZ did not differ for patients with disseminated disease (median of 18.2 months) versus those with localized disease (median of 19 months; $P = .40$).

The incidence rate of first HZ episode after autologous HCT per person years over the entire follow-up period was .06 (95% CI, .05 to .08; Table 3). The highest incidence rate was .13 in the second year. Patients who had all their follow-up with complete medical records at our center had a higher crude incidence of HZ (27.1%) than what was determined for patients outside of our center (18.2%), suggesting a potential underestimation of the overall incidence of HZ in this cohort.

Risk Factors

At the time of first HZ episode, 159 of 194 patients (82%) were clearly documented as no longer receiving ACV/VACV prophylaxis. Of the remaining 35 patients, there was clear documentation that 23 patients were still taking ACV/VACV prophylaxis; the additional 12 patients had follow-up questionnaires after their episode of HZ indicating that they were still taking prophylaxis. Seventeen of the 35 breakthrough cases occurred in the first year after HCT. The median time to first HZ episode after stopping ACV/VACV prophylaxis was 4 months (IQR, 1.7 to 7.3). Of the 194 patients who developed HZ, 69 patients received subsequent ACV/VACV prophylaxis for a median of 11.7 months (IQR, 3.6 to 24.5).