Biol Blood Marrow Transplant 25 (2019) 1642–1647

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Severe Herpes Zoster Requiring Intravenous Antiviral Treatment in Allogeneic Hematopoietic Cell Transplantation Recipients on Standard Acyclovir Prophylaxis

Emily Baumrin[1,*], Matthew P. Cheng[1], Sanjat Kanjilal[1,2,3], Vincent T. Ho[4], Nicolas C. Issa[1,4], Lindsey R. Baden[1,4]

[1] Department of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts
[2] Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts
[3] Department of Infectious Disease, Massachusetts General Hospital, Boston, Massachusetts
[4] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts

Article history:
Received 20 March 2019
Accepted 10 April 2019

Key Words:
Herpes zoster
Varicella zoster virus
Allogeneic transplantation
Acyclovir

A B S T R A C T

Allogeneic hematopoietic cell transplantation (HCT) recipients are at increased risk for varicella zoster virus (VZV) reactivation and associated complications. The incidence, timing, and risk factors for severe herpes zoster (HZ) are not well described in the era of acyclovir (ACV) prophylaxis. We performed a retrospective cohort study of all patients who underwent first allogeneic HCT between October 2006 and December 2015 at our institution. Patients were followed until December 2017 for the development of severe HZ, defined as necessitating administration of i.v. antiviral medication. Out of 2163 patients who underwent allogeneic HCT, 22 (1.0%) developed severe HZ at a rate of 1 per 228 person-years, including dermatomal/multidermatomal disease (n = 5), disseminated skin disease (n = 5), HZ ophthalmicus (n = 4), meningitis/encephalitis (n = 4), pneumonia (n = 2), viremia (n = 1), and erythema multiforme (n = 1). Severe HZ infection occurred in a bimodal distribution during the early peri-HCT period and at 12 to 24 months post-HCT (median, 12.7 months). Twelve patients (54.5%) were compliant with ACV prophylaxis at the time of HZ diagnosis. Eleven patients (50%) died during the study period, only 2 of whom (9.1%) with active VZV infection. Mortality was higher in patients on immunosuppressive therapy (62.5% versus 16.7%; $P = .045$) and with concurrent graft-versus-host disease (75.0% versus 35.7%; $P = .044$). These data suggest that severe HZ remains an important consideration despite ACV prophylaxis.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) recipients frequently experience complications from varicella zoster virus (VZV) infection, which occurs in up to 30% of patients before introduction of acyclovir (ACV) prophylaxis [1-5]. The majority of cases result from viral reactivation in the setting of T cell suppression. Risk factors for allogeneic HCT-associated herpes zoster (HZ) include advanced age, graft-versus-host disease (GVHD), pretransplantation leukemia or lymphoma, and conditioning with total body irradiation or antithymocyte globulin [3,4].

Allogeneic HCT recipients have high rates of severe HZ, including multidermatomal HZ, cutaneous dissemination, or visceral involvement [6-10]. Before the implementation of prolonged ACV prophylaxis for allogeneic HCT recipients, 32% of VZV reactivation episodes were classified as severe [11]. Although antiviral treatment can be initiated in these cases, death from VZV infection has been reported in up to 10% to 20% of patients during hospitalization [4,10,12].

Clinical studies have demonstrated that ACV prophylaxis decreases the rate of HZ reactivation in allogeneic HCT recipients [2,12-19]. ACV prophylaxis is typically recommended for a minimum of 12 months following HCT based on established benefit in the postengraftment period [13,14,20-22]. However, antiviral prophylaxis strategies vary among transplantation centers [12,13,23-25], and increased rates of late VZV infection after cessation of ACV, termed the "rebound effect," have not been definitively shown [12,13,15].

Although studies have shown a reduction in the overall development of HZ with ACV prophylaxis [12-14], the incidence, timing, and disease characteristics of severe HZ have not yet been described. In this study, we evaluated the impact of ACV prophylaxis, immunosuppression, and GVHD on the incidence of severe HZ requiring i.v. antiviral treatment in patients after an allogeneic HCT.

Financial disclosure: See Acknowledgments on page 1647.
* Correspondence and reprint requests: Emily Baumrin, MD, 75 Francis Street, SR-154, Boston, MA 02115.
E-mail address: ebaumrin@partners.org (E. Baumrin).

https://doi.org/10.1016/j.bbmt.2019.04.015
1083-8791/

METHODS

To define the characteristics associated with severe HZ in recipients of allogeneic HCT, we performed a single-center, retrospective cohort study of patients undergoing allogeneic HCT at the Dana-Farber Cancer Institute/Brigham and Women's Hospital. Our study population comprised all patients who underwent first allogeneic HCT between October 2006 and December 2015 with severe HZ (defined below). Our data were derived from a clinical data repository for HCT recipients maintained by the Dana-Farber Cancer Institute and a separate clinical database maintained by the Partners HealthCare system (Research Patient Data Registry). This study was approved by the Dana-Farber/Harvard Cancer Center Office for Human Research Studies.

All allogeneic HCT recipients were given prophylaxis with oral ACV (target dose 400 mg 3 times daily [t.i.d.]) for at least 12 months following HCT during the study period. To confirm ACV prophylactic practices during the 12 to 24 months after HCT, we performed a sensitivity analysis of the study population. We excluded patients who died within 12 months of HCT and selected 10% of the remaining patients by randomized number generator with equal distribution by year of HCT. We performed a manual chart review to determine concordance of ACV prophylaxis and immunosuppressive medications. Prophylaxis was further characterized by drug, route, dose, and patient compliance.

We defined severe cases of HZ as patients with clinical or microbiologic evidence of HZ disease who required administration of a therapeutic dose of i.v. antiviral medication. Clinician notes (telephone, clinic, hospital, and scanned outside records) containing the terms "herpes," "zoster," "varicella," "VZV," "HSV," "shingles," and "chickenpox" were extracted and underwent manual review. A patient was deemed to meet the clinical criteria for severe HZ disease if two or more treating physicians agreed that the patient had the classic dermatomal cutaneous or ophthalmologic examination findings. All patients who were diagnosed with visceral (eg, pneumonia, encephalitis, meningitis) or atypical cutaneous disease were required to have a microbiologic diagnosis. All microbiologic data for the cohort were extracted, and patients with a positive VZV direct fluorescence antigen (Boston Children's Hospital), VZV culture (Brigham and Women's Hospital), or VZV polymerase chain reaction result were considered to have met the microbiological criteria for HZ disease. Molecular testing for VZV was performed at different reference laboratories during the study period, including Focus Diagnostics (Cypress, CA), Arup Laboratory (Salt Lake City, UT), Quest Diagnostics (Chantilly, VA), Viracor-IBT Laboratory (Lee's Summit, MO), and Mayo Clinic (Rochester, MN). Patients with positive VZV serology without signs of symptomatic infection were excluded.

We selected evaluated patient characteristics known to be associated with immune dysfunction and the risk of HZ, including age, sex, type of underlying disease, type of HCT, HLA-matching status, donor relation status, VZV serotype, type of conditioning regimen, and type of GVHD prophylaxis. At the time of HZ diagnosis, we captured the presence of GVHD, the presence and type of immunosuppression, and the use of antiviral prophylaxis. We stratified GVHD by acute versus chronic and by severity.

The primary outcome was the time from allogeneic HCT to the first episode of severe HZ. A secondary outcome was the interval from the onset of HZ to the time of death. Patients were followed through December 31, 2017. The duration of follow-up was determined by a manual chart review of clinician's notes (defined above). Patients were censored for the first episode of HZ, disease relapse, repeat HCT, death, and last patient contact through December 2017. We performed survival analysis with right censoring of events occurring after this date. The log-rank test was used to calculate differences between groups. Statistical calculations were performed using JMP version 14.1.0.

Table 1
Patient Demographic Data

Characteristic	Severe HZ	Allogeneic HCT
Number	22	2163
Sex, male/female, n	12/10	1261/902
Age, yr, median (range)	37 (18-63)	55 (17-76)
Underlying disease, n (%)		
Acute leukemia	8 (36)	994 (46)
Chronic leukemia	3 (14)	221 (10)
Hodgkin lymphoma	2 (9)	66 (3)
Non-Hodgkin lymphoma	2 (9)	342 (16)
Myelodysplastic syndrome	2 (9)	327 (15)
Other*	5 (23)	213 (10)
Stem cell source, n (%)		
PBSCs	15 (68)	1846 (85)
BM	3 (14)	200 (9)
BM + PBSCs	0 (0)	4 (1)
Cord blood	4 (18)	114 (5)
Conditioning regimen, n (%)		
Myeloablative	7 (32)	791 (37)
Reduced intensity	15 (68)	1372 (53)
T cell depleted (CD34 selection), n (%)	1 (5)	15 (1)
Donor type, n (%)		
Related	7 (32)	747 (35)
Unrelated	15 (68)	1416 (65)
HLA typing, n (%)		
Matched (8/8)	15 (68)	1809 (84)
Mismatched	7 (32)	354 (16)
Pretransplantation recipient VZV status, n (%)		
Positive	21 (95)	2022 (93)
Negative	0 (0)	92 (4)
Equivocal	0 (0)	32 (2)
Not performed	1 (5)	16 (1)
Unknown	0 (0)	1 (0)
GVHD prophylaxis, n (%)		
Tacrolimus	20 (91)	2089 (97)
Sirolimus	13 (59)	1178 (54)
Methotrexate	12 (55)	1523 (70)
Mycophenolate mofetil	4 (18)	124 (6)

PBSCs indicates peripheral blood stem cells; BM, bone marrow.
*Other includes i mmunodeficiency (n = 1, 2), multiple myeloma (n = 1, 59), myeloproliferative disorder (n = 2, 71), red cell disorder (n = 1, 65), and other (n = 0, 16).

RESULTS

Between October 2006 and December 2015, 2163 patients underwent first allogeneic HCT, with a total 5011 person-years (PY) of follow-up. Twenty-two patients (1.0%) developed severe HZ infection, with a rate of 1 per 228 PY. After excluding patients who were VZV seronegative (n = 92), the rate was similar (1 per 225 PY). Patient characteristics are presented in Table 1. The median patient age at HCT was 37 years (range, 18 to 63 years), and 12 (54.5%) were male. HZ reactivation occurred at a median of 12.7 months (interquartile range [IQR], 2.1 to 20.9 months) after HCT, with a median follow-up of 51 months (IQR, 21.2 to 92.4 months). Nineteen episodes (86.4%) occurred within 24 months, 11 (50%) of these within the first 12 months (Figure 1). The rate of HZ incidence did not change over the 8-year study period (Figure 2). Twelve patients (54.5%) were receiving ACV prophylaxis at the time of reactivation, and 16 patients (72.7%) were on immunosuppressive medication (Table 2).

We assessed severe HZ for patients receiving standard ACV prophylaxis at 0 to 12 months post-HCT, after additional prophylaxis at 12 to 24 months post-HCT, and after scheduled zoster vaccine (Zostavax; Merck & Co, Whitehouse Station, NJ) at >24 months post-HCT. Of the 11 patients who developed severe HZ within 12 months from HCT, 2 were noncompliant with ACV prophylaxis, 2 were on renally dosed ACV, and 2 were on i.v. ACV prophylaxis due to an inability to take oral medications. Two patients received therapeutic dose valacyclovir and famciclovir for a history of VZV within the year before HCT, and the remaining 3 patients had HZ despite prophylaxis with standard ACV dosing (400 mg p.o. t.i.d.). All 11 patients were on immunosuppression at the time of diagnosis, including 4 (36.4%) on a steroid dose equivalent of >20 mg prednisone per day.

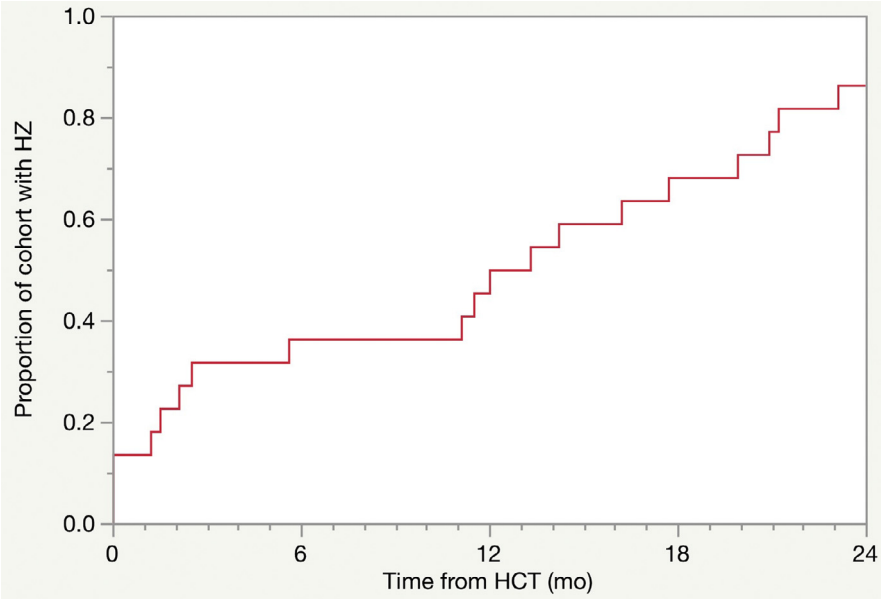

Figure 1. Time to severe HZ infection after HCT. Severe HZ cases censored at 24 months (n = 3). Censored cases occurred at 46, 61, and 82 months after HCT.

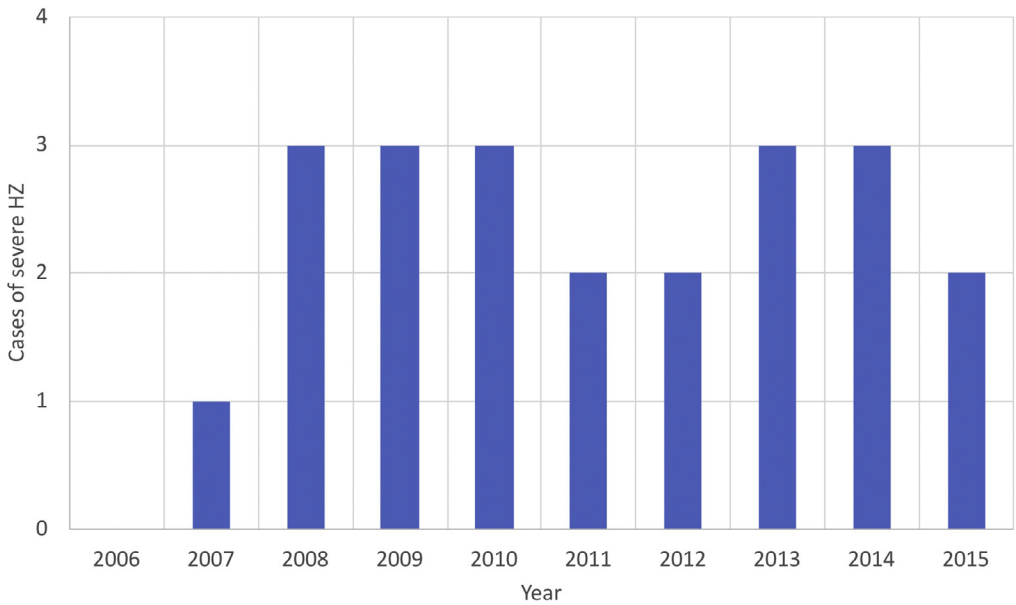

Figure 2. Number of severe HZ cases per study year.

Of the 8 patients who had severe HZ at 12 to 24 months post-HCT, 3 patients were on standard ACV dosing and concurrent immunosuppression for GVHD and the other 5 patients were not on ACV prophylaxis and were not receiving immunosuppressive medications. To confirm ACV prophylaxis deployment, we evaluated 10% of the study population who survived past 12 months (131 of 1309). Ninety-seven patients were on systemic immunosuppression, all of whom were receiving concordant therapy with ACV prophylaxis in accordance with institutional practice guidelines. Of the 34 patients who were not on immunosuppression, 15 were not receiving ACV prophylaxis.

At >2 years post-HCT, 3 patients had severe HZ. Two patients were on immunosuppression for chronic GVHD and kidney transplantation. No patients were taking ACV prophylaxis, and none had received Zostavax. The most common immunosuppressive medications administered at the time of diagnosis were prednisone (71.4%), tacrolimus (71.4%), and sirolimus (42.9%).

Clinical presentations were heterogenous and included dermatomal/multidermatomal HZ (n = 5), disseminated cutaneous HZ (n = 5), HZ ophthalmicus (n = 4), VZV meningitis/encephalitis (n = 4), VZV pneumonia (n = 2), VZV viremia (n = 1), and erythema multiforme with mucosal involvement (n = 1) (Table 3). Three patients were treated with i.v. foscarnet for VZV infection, 2 who were switched from i.v. acyclovir due to disease progression and 1 who was treated with i.v. foscarnet at presentation. No VZV genotyping was performed. Ten of 12 patients (83.3%) on antiviral prophylaxis were treated with i.v. acyclovir and did well. The median duration of i.v. antiviral therapy was 4 days (range, 1 to 38 days), and the median duration of hospitalization was 9 days (range, 1 to 60 days).

Table 2
Characteristics of Patients with Severe HZ Infection

Characteristic	Number (%)
Before HZ	
Acute GVHD	
Yes	9 (41)
Grade I	1 (5)
Grade II	4 (18)
Grade III	3 (14)
Grade IV	1 (5)
No	13 (59)
Chronic GVHD	
Yes	6 (27)
No	16 (73)
Steroid-refractory GVHD	5 (23)
Acute	1 (5)
Chronic	3 (14)
Acute and chronic	1 (5)
At HZ diagnosis	
Antiviral prescription	12 (55)
ACV p.o. 400 mg t.i.d.	6 (27)
ACV p.o. 400 mg b.i.d.	2 (9)
ACV i.v. 200 mg t.i.d.	2 (9)
Famciclovir 500 mg t.i.d.	1 (5)
Valacyclovir 1000 mg t.i.d.	1 (5)
None	10 (45)
Concurrent GVHD	
Yes	8 (36)
Acute	4 (18)
Chronic	3 (14)
Acute and chronic	1 (5)
No	14 (64)
Immunosuppression	16 (73)
Prednisone	10 (45)
Tacrolimus	10 (45)
Sirolimus	6 (27)
Mycophenolate mofetil	5 (23)
Fludarabine/busulfan	1 (5)
Melphalan	1 (5)
None	6 (27)

p.o. indicates orally; t.i.d., 3 times daily; b.i.d., twice daily.

Table 3
Clinical Presentation and Outcomes of Severe HZ

Clinical Outcomes	Value
Method of diagnosis, n (%)	
Microbiological	14 (64)
Clinical	8 (36)
Time to infection from HCT, d, median (IQR)	12.7 (18.1)
Clinical presentation, n (%)	
Dermatomal/multidermatomal	5 (23)
Disseminated cutaneous	5 (23)
Ophthalmicus	4 (18)
Meningitis/encephalitis	4 (18)
Pneumonia	2 (9)
Viremia	1 (5)
Erythema multiforme	1 (5)
Treatment, n (%)	
Acyclovir, i.v.	17 (77)
Foscarnet, i.v.	3 (14)
Valacyclovir, p.o.	2 (9)
Cidofovir, i.v.	2 (9)
Brincidofovir, i.v.*	1 (5)
Duration of treatment, d, median (range)	14 (7-68)
Duration of hospitalization, d, median (range)	10 (1-60)
90-d mortality, n (%)	3 (14)
1-yr mortality, n (%)	7 (32)
Previous HZ within 1 yr of presentation, n (%)	3 (14)

*A s part of the study.

Mortality at 90 days from the development of HZ was 13.6% (Figure 3A), with 9.1% (n = 2) dying with active VZV infection. Mortality from the time of HZ diagnosis was higher in the patients receiving immunosuppressive medications compared with those not receiving immunosuppressive medications (62.5% versus 16.7%; $P = .045$) and in patients with concurrent GVHD compared with those without GVHD (75.0% versus 35.7%; $P = .044$) (Figure 3B and C). Patients on ACV prophylaxis (66.6% versus 30.0%; $P = .052$) and those with dermatomal HZ (80.0% versus 41.2%; $P = .197$) had higher mortality compared with their counterparts, although the difference was not statistically significant.

DISCUSSION

Before implementation of standard 12-month ACV prophylaxis, one-third of VZV reactivation infections were classified as severe, with 40% of episodes necessitating hospitalization [1]. Disseminated skin infection occurred in 15% to 30% of patients [26], and visceral VZV occurred in .8% of patients, with high mortality [10]. Our cohort corroborates the efficacy of ACV prophylaxis, with only 1.0% of patients developing HZ necessitating hospitalization. Furthermore, 5 patients in our cohort had dermatomal or multidermatomal HZ, which might not be considered severe by some [1,11]. The rationale for treating dermatomal HZ with i.v. antivirals was variable; 4 were admitted for >1 indication, including 2 for conditioning, and 1 was monitored while on immunosuppression. Interestingly, dermatomal HZ conferred higher mortality, which may more accurately reflect the risk of having multiple indications for admission. Rates of severe HZ infection did not change over our 10-year study period despite changes in HCT treatment regimens, suggesting the continued efficacy of ACV prophylaxis despite changing practice.

Although rates of severe HZ have decreased with standard 12-month ACV prophylaxis, cases do still occur with significant morbidity and mortality, including in patients on ACV prophylaxis. Two patients on ACV prophylaxis were treated with i.v. foscarnet for presumed VZV resistance; however, 10 patients were treated successfully with higher dose i.v. ACV. Given the lack of VZV resistance testing data, it is difficult to determine whether cases were due to VZV resistance, subtherapeutic serum levels of ACV, or host immunosuppression. Foscarnet should be considered for patients compliant with ACV prophylaxis at the time of HZ; however, our data support that i.v. ACV may work in many cases. Patients on ACV at the time of HZ had higher mortality, although the differnece was not statistically significant. ACV may serve as a marker for sicker patients, who are more likely to be on immunosuppression and have concurrent GVHD.

Severe HZ occurred in a bimodal distribution with an early peak (<90 days) and a late peak (12 to 24 months) post-HCT. Early HZ cases (n = 7) were seen in severely immunocompromised hosts despite ACV prophylaxis. In addition to standard risk factors

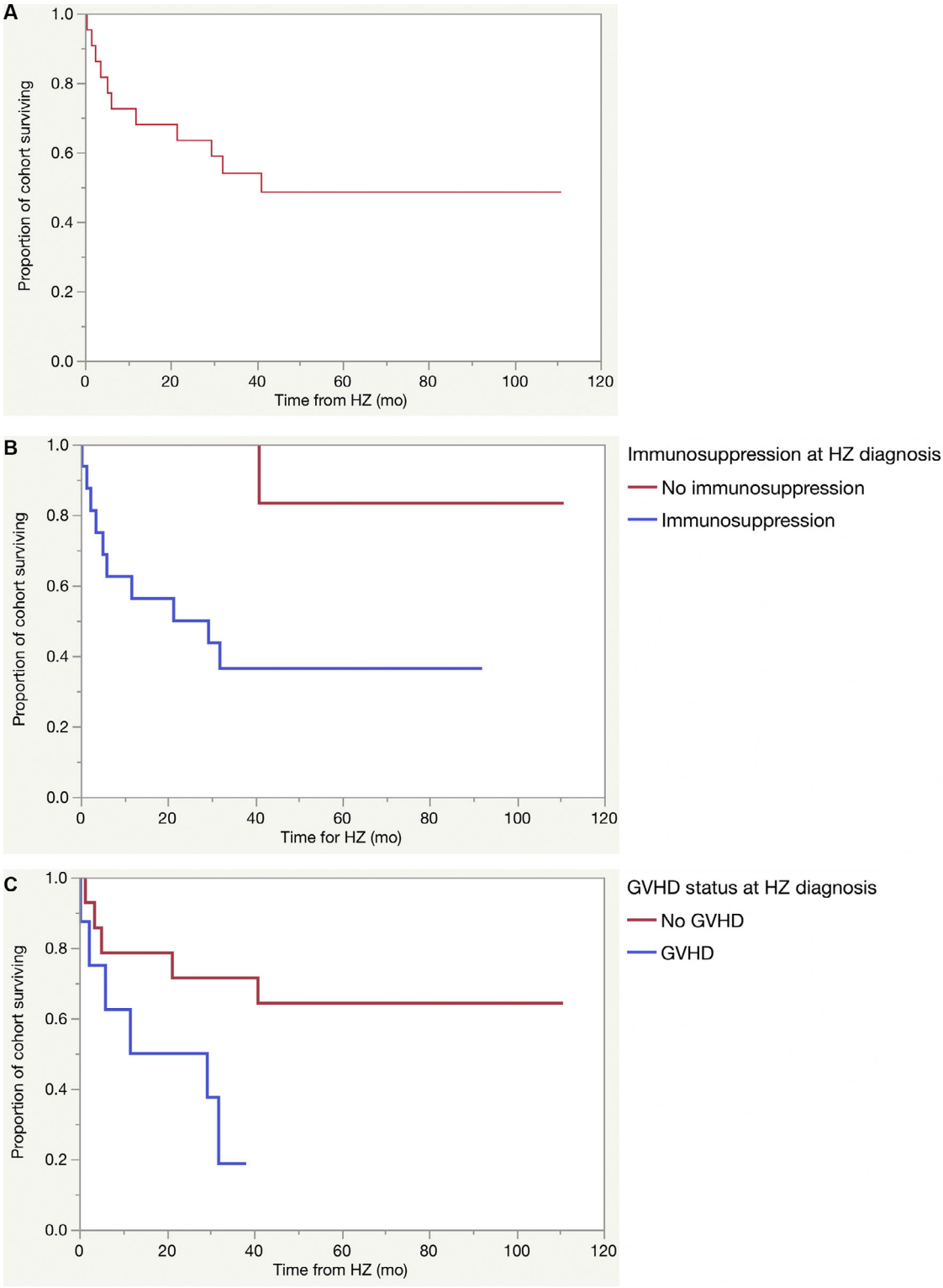

Figure 3. Mortality after severe HZ infection. (A) Overall mortality after severe HZ infection. (B) Mortality after severe HZ infection stratified by status of immunosuppression at time of HZ diagnosis. (C) Mortality after severe HZ infection stratified by GVHD status at time of HZ diagnosis.

in the peri-HCT period, 3 patients were on high-dose steroids for acute GVHD, and 2 patients had reactivation of recent VZV infection with initiation of conditioning. At 3 to 12 months, ACV prophylaxis appears to be highly effective; the single patient who developed severe HZ in this time period was ACV noncompliant.

Late cases peaked at 12 to 24 months post-HCT at which time HZ occurred in patients on ACV prophylaxis and immunosuppression (n = 3) and in those on neither (n = 5). Sensitivity analysis demonstrated that patients on immunosuppression were receiving the standard ACV prophylaxis, although medication compliance was not assessed. Because cases occur in the absence of immunosuppressive medications, patients in this group likely carry additional risk factors, such as delayed adaptive immune reconstitution.

Although before the introduction of standard ACV prophylaxis, the majority of severe HZ cases occurred within 7 months of HCT [11,12], risk now appears to extend beyond the early peri-HCT period. Extending ACV through month 24 in all patients is one method of enhancing pharmacologic prophylaxis; however, cases still occur even with ACV prophylaxis, and 3 times daily dosing limits compliance. HZ vaccination to enhance HZ-specific immune reconstitution has been used in the post-HCT setting [24,27]. The recombinant zoster vaccine was found to be safe and effective in autologous HCT recipients [28,29]; however, immune responses to vaccinations may differ in autologous HCT and allogeneic HCT, and timing, target population, and concomitant use of prophylactic ACV requires further study [30,31].

Our results must be interpreted in the context of the study's retrospective and descriptive nature. This study reflects a single-center experience of adult patients, limiting its generalizability. Although a manual chart review enhanced accuracy, follow-up data was incomplete due to loss to follow-up, discharge from our center, or unreported death. Thus, the incidence rate may be underestimated. Mirroring clinical practice, both clinical and microbiological diagnostic criteria were used, and clinical presentations were heterogeneous. The study had a noncontemporaneous cohort of HCT recipients, with HZ outcomes influenced by changes in best practices and improvement in care over time.

In the era of ACV prophylaxis, severe HZ reactivation was identified in 1.0% (1/228 PY) of HCT recipients. The majority of cases occurred <24 months after HCT and in a bimodal distribution despite prophylactic ACV use in many. Defining the use of HZ vaccination in this population may be an additional means of prophylaxis in this vulnerable group.

ACKNOWLEDGMENTS

Financial disclosure:

Conflict of interest statement: N.C.I. has received research grants from GSK and Merck.

REFERENCES

1. Koc Y, Miller KB, Schenkein DP, et al. Varicella zoster virus infections following allogeneic bone marrow transplantation: frequency, risk factors, and clinical outcome. *Biol Blood Marrow Transplant*. 2000;6:44–49.
2. Kim DH, Kumar D, Messner HA, et al. Clinical efficacy of prophylactic strategy of long-term low-dose acyclovir for varicella-zoster virus infection after allogeneic peripheral blood stem cell transplantation. *Clin Transplant*. 2008;22:770–779.
3. Kim DH, Messner H, Minden M, et al. Factors influencing varicella zoster virus infection after allogeneic peripheral blood stem cell transplantation: low-dose acyclovir prophylaxis and pre-transplant diagnosis of lymphoproliferative disorders. *Transpl Infect Dis*. 2008;10:90–98.
4. Locksley RM, Flournoy N, Sullivan KM, Meyers JD. Infection with varicella-zoster virus after marrow transplantation. *J Infect Dis*. 1985;152:1172–1181.
5. Ho DY, Arvin AM. Varicella zoster virus infections. In: Forman SJ, Negrin RS, Antin JH, Appelbaum FR, eds. *Thomas' Hematopoietic Cell Transplantation: Stem Cell Transplantation*. 5th ed Hoboken, NJ: Wiley-Blackwell; 2016:1046–1065.
6. Walton RC, Reed KL. Herpes zoster ophthalmicus following bone marrow transplantation in children. *Bone Marrow Transplant*. 1999;23:1317–1320.
7. David DS, Tegtmeier BR, O'Donnell MR, Paz IB, McCarty TM. Visceral varicella-zoster after bone marrow transplantation: report of a case series and review of the literature. *Am J Gastroenterol*. 1998;93:810–813.
8. Tauro S, Toh V, Osman H, Mahendra P. Varicella zoster meningoencephalitis following treatment for dermatomal zoster in an alloBMT patient. *Bone Marrow Transplant*. 2000;26:795–796.
9. Takatoku M, Muroi K, Kawano-Yamamoto C, Nagai T, Komatsu N, Ozawa K. Involvement of the esophagus and stomach as a first manifestation of varicella zoster virus infection after allogeneic bone marrow transplantation. *Intern Med*. 2004;43:861–864.
10. Doki N, Miyawaki S, Tanaka M, et al. Visceral varicella zoster virus infection after allogeneic stem cell transplantation. *Transpl Infect Dis*. 2013;15:314–318.
11. Han CS, Miller W, Haake R, Weisdorf D. Varicella zoster infection after bone marrow transplantation: incidence, risk factors and complications. *Bone Marrow Transplant*. 1994;13:277–283.
12. Boeckh M, Kim HW, Flowers ME, Meyers JD, Bowden RA. Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation: a randomized double-blind placebo-controlled study. *Blood*. 2006;107:1800–1805.
13. Erard V, Guthrie KA, Varley C, et al. One-year acyclovir prophylaxis for preventing varicella-zoster virus disease after hematopoietic cell transplantation: no evidence of rebound varicella-zoster virus disease after drug discontinuation. *Blood*. 2007;110:3071–3077.
14. Asano-Mori Y, Kanda Y, Oshima K, et al. Long-term ultra-low-dose acyclovir against varicella-zoster virus reactivation after allogeneic hematopoietic stem cell transplantation. *Am J Hematol*. 2008;83:472–476.
15. Ljungman P, Wilczek H, Gahrton G, et al. Long-term acyclovir prophylaxis in bone marrow transplant recipients and lymphocyte proliferation responses to herpes virus antigens in vitro. *Bone Marrow Transplant*. 1986;1:185–192.
16. Selby PJ, Powles RL, Easton D, et al. The prophylactic role of intravenous and long-term oral acyclovir after allogeneic bone marrow transplantation. *Br J Cancer*. 1989;59:434–438.
17. Thomson KJ, Hart DP, Banerjee L, Ward KN, Peggs KS, Mackinnon S. The effect of low-dose aciclovir on reactivation of varicella zoster virus after allogeneic haemopoietic stem cell transplantation. *Bone Marrow Transplant*. 2005;35:1065–1069.
18. Kanda Y, Mineishi S, Saito T, et al. Long-term low-dose acyclovir against varicella-zoster virus reactivation after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2001;28:689–692.
19. Perren TJ, Powles RL, Easton D, Stolle K, Selby PJ. Prevention of herpes zoster in patients by long-term oral acyclovir after allogeneic bone marrow transplantation. *Am J Med*. 1988;85:99–101.
20. Yahav D, Gafter-Gvili A, Muchtar E, et al. Antiviral prophylaxis in haematological patients: systematic review and meta-analysis. *Eur J Cancer*. 2009;45:3131–3148.
21. Baden LR, Swaminathan S, Angarone M, et al. Prevention and treatment of cancer-related infections, version 2.2016. NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14:882–913.
22. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:427–431.
23. Seo HM, Kim YS, Bang CH, et al. Antiviral prophylaxis for preventing herpes zoster in hematopoietic stem cell transplant recipients: a systematic review and meta-analysis. *Antiviral Res*. 2017;140:106–115.
24. Jamani K, MacDonald J, Lavoie M, et al. Zoster prophylaxis after allogeneic hematopoietic cell transplantation using acyclovir/valacyclovir followed by vaccination. *Blood Adv*. 2016;1:152–159.
25. Pollack M, Heugel J, Xie H, et al. An international comparison of current strategies to prevent herpesvirus and fungal infections in hematopoietic cell transplant recipients. *Biol Blood Marrow Transplant*. 2011;17:664–673.
26. Blennow O, Fjaertoft G, Winiarski J, Ljungman P, Mattsson J, Remberger M. Varicella-zoster reactivation after allogeneic stem cell transplantation without routine prophylaxis: the incidence remains high. *Biol Blood Marrow Transplant*. 2014;20:1646–1649.
27. Issa NC, Marty FM, Leblebjian H, et al. Live attenuated varicella-zoster vaccine in hematopoietic stem cell transplantation recipients. *Biol Blood Marrow Transplant*. 2014;20:285–287.
28. Stadtmauer EA, Sullivan KM, Marty FM, et al. A phase 1/2 study of an adjuvanted varicella-zoster virus subunit vaccine in autologous hematopoietic cell transplant recipients. *Blood*. 2014;124:2921–2929.
29. Sullivan K, Abhyankar S, Campora L, et al. Immunogenicity and safety of an adjuvanted herpes zoster subunit vaccine in adult autologous hematopoietic stem cell transplant recipients: phase 3, randomized, placebo-controlled, ZOE-HSCT clinical trial. *Communication presented at the 44th Annual Meeting of the European Society for Blood and Marrow Transplantation*. Lisbon, PortugalMarch 18-21, 2018.
30. Winston DJ, Mullane KM, Cornely OA, et al. Inactivated varicella zoster vaccine in autologous haemopoietic stem-cell transplant recipients: an international, multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391:2116–2127.
31. Mullane KM, Winston DJ, Wertheim MS, et al. Safety and immunogenicity of heat-treated zoster vaccine (ZVHT) in immunocompromised adults. *J Infect Dis*. 2013;208:1375–1385.