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Live Attenuated Varicella-Zoster Vaccine in Hematopoietic Stem Cell Transplantation Recipients

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Article history:
Received 28 August 2013
Accepted 18 November 2013

Key Words:
Varicella-zoster vaccine
HSCT

A B S T R A C T

Hematopoietic stem cell transplantation (HSCT) recipients are at risk for varicella-zoster virus (VZV) reactivation. Vaccination may help restore VZV immunity; however, the available live attenuated VZV vaccine (Zostavax) is contraindicated in immunocompromised hosts. We report our experience with using a single dose of VZV vaccine in 110 adult autologous and allogeneic HSCT recipients who were about 2 years after transplantation, free of graft-versus-host disease, and not receiving immunosuppression. One hundred eight vaccine recipients (98.2%) had no clinically apparent adverse events with a median follow-up period of 9.5 months (interquartile range, 6 to 16; range, 2 to 28). Two vaccine recipients (1.8%) developed a skin rash (one zoster-like rash with associated pain, one varicella-like) within 42 days post-vaccination that resolved with antiviral therapy. We could not confirm if these rashes were due to vaccine (Oka) or wild-type VZV. No other possible cases of VZV reactivation have occurred with about 1178 months of follow-up. Live attenuated zoster vaccine appears generally safe in this population when vaccinated as noted; the overall vaccination risk needs to be weighed against the risk of wild-type VZV disease in this high-risk population.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) recipients are at increased risk for varicella-zoster virus (VZV) reactivation. VZV disease after HSCT varies depending on type of transplantation (autologous versus allogeneic) but is reported to be as high as 30% to 53%; the highest risk has been reported to occur during the first year after transplantation and may be associated with visceral dissemination [1-8]. Antiviral prophylaxis has been shown to prevent VZV reactivation;

Financial disclosure: See Acknowledgments on page 287.
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1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.11.013

however, the duration of prophylaxis varies between centers [1,3,9]. Even when prolonged antiviral prophylactic strategies are used, the incidence of VZV disease remains increased in HSCT recipients, with increased risk for reactivation after prophylaxis is discontinued [9-11]. In 1 study the incidence of VZV in allogeneic HSCT recipients occurring after 12 months of acyclovir prophylaxis was 5% by year 1 after HSCT, 21% by year 2, 29% by year 3, and 37% by year 5 [3].

Boosting immunity against VZV after HSCT through vaccination may help decrease the risk of reactivation. However, limited data are available on the safety and immunogenicity of licensed VZV vaccines in adult HSCT recipients [12]. Guidelines [13,14] have recommend the use of varicella vaccine (Varivax Merck & Co., INC, Whitehouse Station, NJ) in HSCT recipients who have met criteria for live virus vaccination. These recommendations are based on expert opinion that assumes this vaccine, which has lower viral titers compared with the zoster vaccine (Zostavax), may be safer [13]. We report our experience using the zoster vaccine in HSCT recipients.

METHODS

As part of an update in vaccine guidelines in July 2011, autologous and allogeneic HSCT recipients followed at Dana-Farber Cancer Institute were considered for zoster vaccine if they were about 24 months after HSCT, free of graft-versus-host disease (allogeneic), on no immunosuppression, and not taking prophylactic antivirals (acyclovir, valacyclovir, or famciclovir). The recommendation to use the zoster vaccine was made by a multidisciplinary team given the high risk of VZV reactivation in this population after prophylaxis discontinuation and the increased morbidity from VZV in this population, including the development of postherpetic neuralgia. This recommendation followed the approach for administration of other live attenuated vaccines such as the measles-mumps-rubella (MMR) vaccine.

Patients who met these criteria were given a single dose (0.65 mL) of Zostavax (Merck & Co, INC, Whitehouse Station, NJ) containing a minimum of 19,400 plaque-forming units administered subcutaneously at the discretion of their treating physician. Patient's characteristics were recorded. We followed patients for at least 42 days after vaccination. Data were collected through November 6, 2013. Adverse events were captured by reviewing medical records and contacting the patients' primary oncologists. This study was approved by the Office for Human Research Studies at Dana-Farber/Harvard Cancer Center.

RESULTS

One hundred ten patients received zoster vaccine between July 2011 and September 2013. Baseline characteristics are summarized in Table 1. Fifty-eight patients (52.7%) underwent allogeneic HSCT, and 52 patients (47.3%) underwent autologous HSCT. Other characteristics are outlined in Table 1.

Median follow-up time was 9.5 months (interquartile range, 6 to 16; range, 2 to 28). One hundred eight patients (98.2%) had no clinically apparent adverse events. Seventy-six patients received MMR vaccine on the same day zoster vaccine was administered. There were no reported cases of VZV reactivation in any patient occurring after the initial 42 days post-vaccination or during follow-up (0 cases/1178 person-months). No graft-versus-host disease flares were noted in allogeneic HSCT recipients within 42 days post-vaccination.

Two patients developed skin rashes within 42 days after vaccination. Both patients had positive VZV serology before transplantation. The first patient, a 46-year-old woman who underwent allogeneic HSCT 34 months before receiving zoster vaccination in the left upper arm, developed a skin rash 10 days after vaccination. Her absolute lymphocyte count at the time of vaccination was 2.6 K/μL. No CD4 count was performed before vaccination. She did not receive MMR vaccine on the same day. Her local physician reported a dermatomal rash involving the right side of her chest. She was treated with oral acyclovir. She developed postherpetic neuralgia that required treatment with gabapentin. No samples could be obtained to determine if the rash was due to wild-type or vaccine virus. At a 6-month follow-up, the neuralgia had markedly improved.

Table 1
Patient Baseline Characteristics

Characteristic	Value
No. of patients	110
Median age, yr (IQR; range)	58.5 (49-64; 22-74)
Male sex (%)	66 (60.0)
Median months from transplantation (IQR; range)	27 (24-41; 21-98)
Median months of follow-up after vaccination (IQR; range)	9.5 (6-16; 2-28)
HSCT indication	
Lymphoma (%)	40 (36.4)
Leukemia (%)	30 (27.3)
Multiple myeloma (%)	27 (24.5)
Other* (%)	13 (11.8)
Type of stem cell transplantation	
Allogeneic (%)	58 (52.7)
Autologous (%)	52 (47.3)
Pretransplant VZV serology	
Positive	99 (90.1)
Equivocal	4 (3.6)
Negative	6 (5.4)
Unknown	1 (.9)

IQR indicates interquartile range.
* Myelodysplastic syndrome (n = 7), aplastic anemia (n = 5), Waldenström's macroglobulinemia (n = 1).

The second patient, a 38-year-old woman who underwent autologous HSCT 25 months before receiving zoster vaccination, had an absolute lymphocyte count at the time of vaccination of 1.8 K/μL. No CD4 count was performed before vaccination. She received MMR vaccine on the same day as the zoster vaccine. She developed a vesicular skin rash involving the upper extremities and the trunk 24 days after vaccination. Her local physician diagnosed her with zoster and prescribed a course of valacyclovir. No samples could be obtained to confirm if the rash was due to VZV or other causes. At a 4-month follow-up visit she was well.

DISCUSSION

Given the lack of data-driven recommendations in the current guidelines for zoster vaccine in adults after HSCT, we implemented a vaccine schedule that uses the zoster vaccine. Based on the VZV incubation period and previously published zoster vaccine studies, the first 42 days after vaccination was chosen as the primary safety risk assessment period [10,15]. One hundred eight HSCT recipients (98.2%) had no clinically identifiable adverse events after vaccination. In the 2 patients who developed a skin rash after vaccination, we could not confirm that the rash was caused by the vaccine strain. In the first patient, the rash developed 10 days after vaccination and was consistent with zoster given dermatomal presentation and ensuing postherpetic neuralgia. No additional cases of zoster were identified after the 42 day post-vaccine window, with 1178 months of follow up.

In the Zostavax Efficacy and Safety Trial study [15] that enrolled 22,439 subjects, 34 patients overall (.15%) had zoster-like rashes (19 in the vaccine arm, 15 in the placebo arm) within the 42-day post-vaccination reporting period. Wild-type VZV was detected in 3 subjects in the vaccine group and in 7 subjects in the placebo groups. The Oka strain was not

detected. Of the 124 cases (.55%) of varicella-like rashes reported within 42-day post-vaccination, only 1 specimen had VZV detected (zoster vaccine arm); however, it could not be determined if it was a wild-type or vaccine virus. In the Shingles Prevention Study study [10], 53 subjects of 38,546 enrolled (19,270 received vaccine, 19,276 received placebo) had zoster-like rashes (17 vaccine, 36 placebo). Wild-type VZV was detected in 25 specimens (5 in the vaccine group, 20 in the placebo), and the Oka strain was not detected.

The incubation period for an Oka strain–associated dermatomal herpes zoster seemed to be very short in our first patient. In previous studies, rash after vaccination due to wild-type VZV occurred at a median of 8 days after vaccination (range, 1 to 20), whereas Oka strain–related rash occurred at a median of 21 days (range, 5 to 42) [10,16]. In our second patient, the presentation suggested a varicella-like rash. In clinical trials of Varivax conducted in VZV-seronegative children, adolescent, and adults, the reported incidence of varicella-like rash was 3% to 5% [17-23]. Both types of rashes (zoster and varicella-like) were observed in the 2 large zoster vaccination studies (Zostavax Efficacy and Safety Trial and Shingles Prevention Study). In both trials, the skin rashes occurred in both the vaccine and placebo arms, and the presence of the Oka strain could not be demonstrated in any of these rashes. Most cases were due to wild-type VZV occurring in both the placebo and vaccine arms [10,15]. It is worth noting that our population is at a higher risk for VZV reactivation compared with the general population enrolled in both trials. It is also notable that no cases of shingles have been identified to date in any of our vaccinated patients after the 42 day post-vaccination conventional safety period; however, the follow-up time is limited.

This study has some limitations. VZV serology was not performed before vaccination, and post-vaccination immune responses and efficacy were not directly assessed because this study was observational in nature. Given the small sample size, less common safety events would not be detected. Longer follow-up is warranted to see if the vaccine provided clinical efficacy in patients who received it. Because it remains unclear whether Varivax or Zostavax may be better in HSCT recipients from a safety and immunogenicity standpoint, further studies are warranted.

ACKNOWLEDGMENTS

Financial disclosure: Supported in part by the R J Corman research fund.

Conflict of interest statement: N.C.I. and F.M.M. have received research grants from GlaxoSmithKline. F.M.M. has received consulting fees from GlaxoSmithKline and Merck for unrelated work.

Authorship statement: N.C.I., F.M.M., and L.R.B. came up with the study concept and design. M.M.S., H.L., A.G., and N.C.I. acquitted the data. A.G. and F.M.M. performed the statistical analysis. N.C.I. drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

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