Immunogenicity and Safety of a Live Herpes Zoster Vaccine in Hematopoietic Stem Cell Transplant Recipients

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Research article

Keywords: Herpes zoster, Varicella zoster virus, Hematopoietic stem cell transplantation, Immunogenicity, Safety
Abstract

Background

Herpes zoster (HZ) infection of hematopoietic stem cell transplant (HSCT) patients is of clinical concern. Vaccination could help restore immunity to varicella zoster virus (VZV); however, the immunogenicity and safety of live HZ vaccines in patients with hematologic malignancy is unclear. The aim of this study was to elucidate temporal immunogenicity of the HZ vaccine after HSCT and determine the safety and optimal timing of vaccination.

Methods

Live HZ vaccine was administered to patients 2–5 years or >5 years post-HSCT. Control groups comprised healthy volunteers and patients with a hematologic malignancy who received cytotoxic chemotherapy. Humoral and cellular immunogenicity were measured using a glycoprotein enzyme-linked immunosorbent assay (gpELISA) and an interferon-γ (IFN-γ) enzyme-linked immunospot (ELISPOT) assay. Vaccine-related adverse events were also monitored.

Results

Fifty-six patients with hematologic malignancy and 30 healthy volunteers were enrolled. The geometric mean fold rise (GMFR) in humoral immune responses of the 2–5 year and >5 year HSCT groups, and the healthy volunteer group, were comparable and significantly higher than that of the chemotherapy group (3.15, 95% CI [1.96-5.07] vs 5.05, 95% CI [2.50-10.20] vs 2.97, 95% CI [2.30-3.83] vs 1.42, 95% CI [1.08-1.86]). The GMFR of cellular immune responses was highest in the HSCT 2–5 year group and lowest in the chemotherapy group. No subject suffered clinically significant adverse events or reactivation of VZV within the follow-up period.

Conclusion

Our findings demonstrate that a live HZ vaccine is immunogenic and safe when administered 2 years post-HSCT.

Background

Herpes zoster (HZ), also called shingles (derived from Latin cingulus meaning girdle), is a dermatomal-vesicular disease associated with severe pain [1]. It is caused by reactivation of latent varicella zoster virus (VZV) within sensory ganglia and is more common in immunocompromised patients [1]. The incidence of HZ increases with age; the highest incidence (5–10 cases per 1,000 persons) occurs in the sixth decade or beyond [2]. The burden of HZ for those with a hematopoietic stem cell transplant (HSCT) is 20–53% overall; the greatest risk (94 cases per 1,000 person-years) occurs within 2 years of HSCT [3–5].
There are no clear guidelines regarding live vaccination after HSCT. With respect to HZ vaccines, limited data support vaccination after HSCT due to concerns about vaccine-induced VZV infection and lack of evidence regarding vaccine-induced immunogenicity [6–8]. Vaccination against HZ might be considered only when 24 months have elapsed since HSCT, and only in recipients showing no signs of graft-versus-host disease (GvHD) or relapse, and in those not taking immunosuppressants [9–11]. The most recent guidelines from the 2017 European Conference on Infections in Leukaemia (ECIL 7) oppose administration of live HZ vaccines; instead, they recommend antiviral agents to prevent VZV reactivation [12]. However, even with prolonged administration of antiviral agents, the incidence of HZ increases after discontinuation of prophylaxis [4, 13].

Although necessary, there is not enough evidence to support a minimum interval between transplantation and vaccination. A theoretical minimum of 24 months supposes that the HSCT recipient is immunocompetent 2 years after HSCT [14]. Here, we explored the temporal immunogenicity and safety profile of a HZ vaccine in HSCT patients. Patients were divided into two groups: those who received HSCT within 2–5 years from the study point, and those who underwent HSCT more than 5 years ago. This classification was intended to derive practical recommendations for the optimal timing of HZ vaccination in HSCT patients.

Although correlates of protection (CoP) for HZ vaccines are not defined clearly, fold rises in glycoprotein enzyme-linked immunosorbent assay (gpELISA) titers are thought to be an excellent immune correlate of protection [15]. In addition to this measure of humoral immunity, we also assessed cellular immune responses using an interferon-γ (IFN-γ) enzyme-linked immunospot (ELISPOT) assay.

**Methods**

**Study Design**

This was a prospective observational study conducted at Seoul National University Hospital (SNUH), which is a tertiary care university-affiliated hospital in South Korea. The study period spanned July 2018 to June 2019.

Individuals aged > 50 years, who were diagnosed with a hematologic malignancy and had been cured with either autologous or allogeneic HSCT, were eligible. These patients were stratified according to time since transplantation: 2–5 years and > 5 years (hereafter referred to as HSCT 2–5 year and HSCT > 5 year, respectively). Controls included patients with a hematologic malignancy who had undergone cytotoxic chemotherapy and were cured, without relapse for at least 6 months (referred to hereafter as the chemotherapy group). Moreover, healthy volunteers with normal immune status were recruited (referred to hereafter as the healthy group). Exclusion criteria included GvHD, use of immunosuppressants or antiviral agents, HZ reactivation within 1 year of the study period, or receipt of HZ vaccines. All eligible cases were screened during the study period.
Participants who met eligible criteria were given a single dose (0.65 mL) of ZOSTAVAX®. Blood samples were collected to test both humoral and cellular immune responses against VZV prior to vaccination and at 6 weeks post-vaccination. Baseline characteristics included age, sex, underlying diseases, type of HSCT or cytotoxic chemotherapy, and previous history of HZ.

**Glycoprotein ELISA (gpELISA)**

VZV-specific antibodies were measured quantitatively using a SERION ELISA classic Varicella Zoster Virus IgG kit (Institut Virion/Serion GmbH, Würzburg, Germany). This gpELISA assay uses a lentil-lectin affinity-purified preparation of glycoprotein from VZV-infected MRC-5 cells as the antigen [16, 17]. Antigen-coated 96-well plates were incubated with test sera. Human immunoglobulin G antibodies (IgGs) bound to antigen were detected by incubation with anti-human IgG antibodies. Color was developed after reaction with a substrate. Optical density was read at 405 nm.

**ELISPOT Assay**

Peripheral blood mononuclear cells (PBMCs) collected and frozen during the study period were tested using a BD™ IFN-γ ELISPOT kit (BD Bioscience, San Jose, CA, USA). Briefly, PBMCs were activated with VZV and exposed to control antigens on anti-IFN-γ coated plates. After washing, a solution containing a biotinylated anti-IFN-γ detection antibody was added to each well, and streptavidin-HRP solution and substrate were used for color development. Spots were counted with a CTL-ImmunoSpot® reader (CTL ImmunoSpot, Cleveland, OH, USA) and reported as the net number of VZV-specific IFN-γ spot-forming cells (sfc) per 10⁶ PBMCs (the difference between responses to VZV antigen and control antigen) [18]. Samples lacking sufficient PMBCs and results with phytohemagglutinin responses < 300 sfc were not included in the analysis [19].

**Safety**

All vaccinated individuals were evaluated for adverse events using a self-reported structured questionnaire administered 6 weeks post-vaccination. The type and severity of local and systemic adverse events were assessed. Adverse events were graded on a standard scale [20]. The causality of an adverse event after immunization was classified as follows: unlikely (inconsistent), possible (indeterminate), or likely (consistent) [21]. Subjects also informed the study nurse or physician if they noticed any serious adverse reactions immediately after vaccination.

**Statistical Analysis**

For continuous variables, mean (standard deviation, SD) and median (interquartile range, IQR) were used for normally and abnormally distributed data. Categorical variables were expressed as numbers and
percentages. A *t*-test was used to compare continuous variables and the Chi-square or Fisher’s exact test was used to compare categorical variables. One-way ANOVA with Dunnett’s adjustment or Kruskal-Wallis test were used to calculate *P*-values for comparisons of more than two variables. All tests were two-sided and *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS for Windows (version 22; IBM Corp., Armonk, NY, USA).

**Results**

**Baseline Characteristics**

The study screened 60 hematology patients at baseline; four patients dropped out due to follow-up loss (n = 3) and disease recurrence (n = 1). Among the remaining 56 subjects, 26 were assigned to the HSCT 2–5 year group and 15 to the HSCT > 5 year group. The chemotherapy group included 15 patients. In addition, 30 healthy volunteers were enrolled (Fig. 1).

Participants in each group were balanced by age; however, the male-to-female ratio of the healthy group was lower (1:2) than that in the other groups (Table 1). Leukemia and lymphoma were the most common (>50% of participants in each group) underlying malignancies. Twenty patients in the HSCT 2–5 year group (77%), and nine in the HSCT > 5 year group (60%) underwent allogeneic HSCT. A history of HZ reactivation was documented in all study groups except the healthy group. Twelve patients in the HSCT 2–5 year group (46%), nine in the HSCT > 5 year group (60%), and six in the chemotherapy group (40%) had shingles before enrollment in the study (Table 1).
Table 1
Baseline Characteristics

|                                      | HSCT 2–5 yr (n = 26) | HSCT > 5 yr (n = 15) | Chemotherapy (n = 15) | Healthy (n = 30) |
|--------------------------------------|----------------------|----------------------|-----------------------|-----------------|
| Median age, year (IQR)               | 60 (9)               | 58 (9)               | 64 (12)               | 61 (9)          |
| Male sex, n (%)                      | 15 (58%)             | 9 (60%)              | 10 (67%)              | 10 (33%)        |
| HSCT indication, n (%)               |                      |                      |                       |                 |
| Leukemia                             | 11 (42%)             | 4 (27%)              | 14 (93%)              | N/A             |
| Lymphoma                             | 2 (8%)               | 7 (47%)              |                       |                 |
| Multiple myeloma                     | 6 (23%)              | 1 (6.5%)             |                       |                 |
| Myelodysplastic syndrome             | 4 (15%)              | 2 (13%)              |                       |                 |
| Others*                              | 3 (12%)              | 1 (6.5%)             | 1 (7%)                |                 |
| Type of HSCT, n (%)                  |                      |                      |                       |                 |
| Allogeneic                           | 20 (77%)             | 9 (60%)              | N/A                   | N/A             |
| Autologous                           | 6 (23%)              | 6 (40%)              |                       |                 |
| Time since HSCT, months (IQR)        | 36 (25–43.5)         | 86 (65.5–90.5)       | N/A                   | N/A             |
| Previous Shingles history, yes, n (%)| 12 (46%)             | 9 (60%)              | 6 (40%)               | 0 (0%)          |
| Median years from Shingles (IQR; range) | 2.6                  | 5.2                  | 8.2                   | N/A             |

IQR, interquartile range; yr, year; N/A; not applicable

*Aplastic anemia (n = 3), Myeloid sarcoma (n = 1), Granulocytic sarcoma (n = 1)

Humoral Immune Responses

At baseline, the gpELISA geometric mean titers (GMT) in the HSCT 2–5 year, chemotherapy, and healthy groups were similar; values were significantly lower in the HSCT > 5 year group (p = 0.041) (Table 2). At 6 weeks post-vaccination, immune responses measured in the gpELISA increased significantly in all four groups, compared with the baseline (Fig. 2A). The GMFR in the chemotherapy group was significantly lower than in the other groups (1.42; 95% CI, 1.08–1.86) (Fig. 2C). The GMFR of the HSCT 2–5 year, HSCT > 5 year, and healthy groups were not significantly different (Fig. 2C).
### Table 2
Humoral and cellular responses after Herpes Zoster vaccination

|                  | gpELISA | ELISpot |
|------------------|---------|---------|
|                  | Sample (n) | Sample (n) |
| HSCT 2–5 yr (n = 26) | 26 | 12 |
| HSCT > 5 year (n = 15) | 15 | 7 |
| Chemotherapy (n = 15) | 15 | 13 |
| Healthy (n = 30) | 30 | 20 |

|                  | GMT, mIU/mL (95% CI) | GMFR in gpELISA (95% CI) | GMC (95% CI) | GMFR in ELISpot (95% CI) |
|------------------|----------------------|--------------------------|--------------|--------------------------|
|                  | Baseline             | Week 6                  | Baseline     | Week 6                  |
| gpELISA          | 841.08 (439.58–1609.29) | 2653.12 (1529.78–4601.33) | 9.00 (3.43–23.60) | 8.39 (3.30–21.32) |
|                  | 262.89 (149.59–462.00) | 1327.03 (615.44–2861.35) | 27.99 (8.45–92.65) | 5.08 (1.86–13.86) |
|                  | 515.92 (302.03–881.28) | 732.57 (390.26–1375.13) | 14.76 (6.57–33.16) | 1.64 (1.23–2.17) |
|                  | 657.15 (424.18–1018.09) | 1949.19 (1395.23–2723.11) | 51.39 (34.36–76.88) | 1.82 (1.32–2.49) |

Data represent overall responses (units per mL in the gpELISA or counts per 10⁶ peripheral blood mononuclear cells in the interferon-γ ELISPOT assay) with 95% confidence intervals.

**HSCT**, hematopoietic stem cell transplantation; **N**, number; **gpELISA**, glycoprotein ELISA; **Interferon-γ ELISPOT**, interferon-γ enzyme-linked immunospot assay; **GMT**, geometric mean titer of varicella zoster virus-specific IgG; **GMFR**, geometric mean fold rise; **GMC**, geometric mean concentration of interferon-γ-secreting varicella zoster virus-specific peripheral blood mononuclear cells

**Cellular Immune Responses**
At baseline, the geometric mean concentrations (GMC) of IFN-γ-secreting VZV-specific PBMCs were higher in the healthy group than in the other three groups \( (p = 0.006) \) (Table 2). Six weeks post-vaccination, the GMC of IFN-γ-secreting VZV-specific PBMCs increased significantly in all groups, with the HSCT > 5 year group showing the highest value \( (142.12; 95\% \text{ CI}, 42.12–479.50) \) (Fig. 2B). The GMFR of the IFN-γ ELISPOT assay was highest in the HSCT 2–5 year group and lowest in the chemotherapy group (Fig. 2D).

**Safety**

There were no reported cases of VZV reactivation up to 6 weeks post-vaccination in any of the study groups. Injection site reactions such as local pain, redness, edema, and itching were the most common adverse events reported by vaccine recipients (Table 3). Three patients in the HSCT 2–5 year group \( (11.5\%) \) and one each in the HSCT > 5 year \( (6.6\%) \) and chemotherapy \( (6.6\%) \) groups reported vaccine-related systemic adverse events such as headache, myalgia, and fatigue (Table 3). All adverse events were mild (grade 1) and occurred within 7 days of vaccination.
## Table 3
### Adverse Events

|                      | HSCT 2–5 yr (n = 26) | HSCT > 5 year (n = 15) | Chemotherapy (n = 15) | Healthy (n = 30) |
|----------------------|----------------------|------------------------|-----------------------|------------------|
| Any adverse events, n (%) | 5 (19.2)             | 3 (20.0)               | 2 (13.3)              | 0 (0)            |
| Local adverse events, n (%) | 4 (15.4)             | 2 (13.3)               | 1 (6.6)               | 0 (0)            |
| Pain or tenderness | 3 (11.5)             | 2 (13.3)               | 1 (6.6)               | 0 (0)            |
| Redness | 3 (11.5)             | 2 (13.3)               | 1 (6.6)               | 0 (0)            |
| Induration or edema | 1 (3.8)              | 2 (13.3)               | 1 (6.6)               | 0 (0)            |
| Itching | 3 (11.5)             | 2 (13.3)               | 1 (6.6)               | 0 (0)            |
| Systemic adverse events, n (%) | 3 (11.5)             | 1 (6.6)               | 1 (6.6)               | 0 (0)            |
| Headache | 1 (3.8)             | 1 (6.6)               | 0 (0)                 | 0 (0)            |
| Myalgia or arthralgia | 3 (11.5)             | 1 (6.6)               | 0 (0)                 | 0 (0)            |
| Fatigue | 3 (11.5)             | 0 (0)              | 1 (6.6)               | 0 (0)            |
| Fever | 0 (0)              | 0 (0)                | 0 (0)                 | 0 (0)            |
| Systemic allergic reaction | 0 (0)              | 0 (0)                | 0 (0)                 | 0 (0)            |
| Nausea or vomiting | 0 (0)              | 0 (0)                | 0 (0)                 | 0 (0)            |
| Diarrhea | 0 (0)              | 0 (0)                | 0 (0)                 | 0 (0)            |

HSCT, hematopoietic stem cell transplantation; N, number

## Discussion

HZ is a high burden of disease among HSCT recipients whose immune status has been shut down and then slowly reconstituted. Here, we demonstrated that a live HZ vaccine could be administered safely to hematologic malignancy patients, and that it induced humoral and cellular immune responses as strong as those in healthy individuals. A previous study examined HZ vaccine-induced immunity in the general population, and we found that humoral and cellular immune responses in the healthy group were similar to those reported in that study [22].

Interestingly, vaccine-induced humoral and cellular GMFR responses in the HSCT groups were higher than in the chemotherapy group. Furthermore, the results indicate that baseline humoral and cellular immunity against VZV in the HSCT > 5 year group was much lower than in the chemotherapy and healthy groups, highlighting the need for prompt vaccination of HSCT recipients. Post-vaccination immunity in the HSCT groups was comparable with that in the healthy group. Previously, we reported that impaired cell-
mediated immunity in multiple myeloma patients treated with chemotherapy led to a significantly increased risk for HZ infection [19].

Two previous studies of HZ vaccines administered at a median 21–27 months post-transplantation reported that it was safe, and that it reduced the incidence of VZV infection [4, 23]. Here, we found no VZV reactivation after administration of a live HZ vaccine to patients with a hematologic malignancy. Vaccine-related adverse reactions, both local and systemic, were more common in patients than in healthy volunteers; however, none were severe. Patients with hematologic malignancy might be more sensitive than healthy volunteers to adverse events and more prone to report mild symptoms. All patients recovered spontaneously within 1 week after immunization.

The study has some limitations. First, fewer patients qualified for the ELISPOT assay than for the gpELISA due to lack of sufficient blood. Inevitably, this led to a lack of statistical power when analyzing differences between groups. Second, patients in the HSCT > 5 year group had fewer members that the other groups; this was due to survival and recurrence rates, chronic GvHD, and other medical issues. Third, two inactive HZ vaccines have been introduced recently, and the published safety and efficacy data seem very strong [24, 25]. Unfortunately however, neither vaccine is available in most countries, including South Korea. Further studies of cost-effectiveness are needed. In practical terms, we expect to continue using live VZV vaccines (at least for a few years); therefore, the immunogenicity and safety data presented herein will be useful in clinical practice.

**Conclusions**

In summary, the HZ vaccine could induce both humoral and cellular immune responses in patients undergoing HSCT, comparable to those in healthy volunteers. Hematologic malignancy patients who were undergoing cytotoxic chemotherapy showed weaker immune responses against the HZ vaccine. There was no reactivation of VZV during follow-up (up to 6 weeks post-immunization), and all reported adverse events were mild. These findings support current guidelines stating that live HZ vaccines may be administered to patients 2 years post-HSCT [9–11].

**Abbreviations**

**HZ:** Herpes zoster  
**HSCT:** Hematopoietic stem cell transplant  
**VZV:** Varicella zoster virus  
**GvHD:** Graft-versus-host disease  
**gpELISA:** Glycoprotein enzyme-linked immunosorbent assay  
**ELISPOT:** Interferon-γ (IFN-γ) enzyme-linked immunospot
Declarations

Ethical Approval

The study was approved by the Institutional Ethics Review Board of SNUH (No. 1705-030-852). All subjects participated in the study supplied informed written consent.

Consent for Publication

Not applicable.

Data Availability

All included data are available from the corresponding author upon request.

Conflict of Interest Disclosure

The authors declare no competing interests.

Funding

This study was supported by the SNUH Research Fund [grant no 03-2017-0360].

Author contributions

WBP and IHK designed the study protocol. CYJ, KCK, MKL, CKK, YIK, DYS, JSH and SSY participated in the data collection and the interpretation of data. PGC, NJK and MDO advised on data analysis and interpretation. CYJ and KCK drafted the manuscript. WBP revised the manuscript and finalized it. All authors read and approved the final manuscript.
Acknowledgements

We thank Su-Jin Choi (Laboratory of Infection & Immunity, Seoul National University Hospital Biomedical Research Institute, Seoul, Korea) for technical assistance.

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