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Safety and Seropositivity after Live Attenuated Vaccine in Adult Patients Receiving Hematopoietic Stem Cell Transplantation

Takatoshi Aoki[1], Tomohiko Kamimura[1], Shuro Yoshida[2], Yasuo Mori[3], Masanori Kadowaki[4], Kentaro Kohno[5], Daisuke Ishihara[1], Shingo Urata[1], Takeshi Sugio[3], Kenjiro Kamezaki[3,6], Koji Kato[3], Yoshikiyo Ito[1,7], Tetsuya Eto[2], Koichi Akashi[3], Toshihiro Miyamoto[3,*]

[1] *Department of Hematology, Harasanshin Hospital, Fukuoka, Japan*
[2] *Department of Hematology, Hamanomachi Hospital, Fukuoka, Japan*
[3] *Department of Medicine and Biosystemic Science, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan*
[4] *Department of Hematology, National Kyushu Medical Center, Fukuoka, Japan*
[5] *Department of Hematology/Oncology, Japan Community Health Care Organization Kyusyu Hospital, Kitakyushu, Japan*
[6] *Department of Internal Medicine, Kyusyu University Beppu Hospital, Beppu, Japan*
[7] *Department of Hematology, Imamura General Hospitals, Kagoshima, Japan*

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A B S T R A C T

Vaccination against vaccine-preventable diseases (VPDs) is highly recommended for hematopoietic stem cell transplantation (HSCT) recipients by several guidelines; however, the safety and seropositivity after live attenuated vaccines remain unclear in adult HSCT recipients. We analyzed titers of antibodies against measles, rubella, mumps, and varicella zoster virus (VZV) from Japanese adult patients who underwent allogeneic HSCT (allo-HSCT) (n = 74), autologous HSCT (auto-HSCT) (n = 39), or chemotherapy (n = 93). The seropositive rates for measles, rubella, mumps, and VZV in allo-HSCT recipients were 20.2%, 36.4%, 5.4%, and 55.4%, respectively. These rates were equivalent to those in auto-HSCT recipients but were significantly lower than those in patients receiving chemotherapy. Antibody titers tended to gradually decrease with time. Twenty-nine allo-HSCT recipients and 8 auto-HSCT recipients received live attenuated vaccines against VPDs for which they tested seronegative. The titers of antibodies against measles, rubella, and mumps significantly increased after 2 shots of vaccine, and the seropositive rate increased up to 19%, 30%, and 27%, respectively. Three patients (8.1%) experienced mild adverse events, which resolved promptly, indicating safe administration of the live attenuated vaccines. In multivariate analysis, history of chronic graft-versus-host disease was significantly associated with high seropositivity for measles as well as high seroconversion rate for measles after vaccination. Live attenuated vaccines against VPDs were safely administered in seronegative adult HSCT recipients. A further observational study is crucial to evaluate the efficacy of vaccination in seronegative HSCT patients.

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INTRODUCTION

Several guidelines for vaccination of the immunocompromised host recommend that recipients of autologous and allogeneic hematopoietic stem cell transplantation (HSCT) receive vaccination against vaccine-preventable diseases (VPDs) [1–4]. Long-term survivors after HSCT can eventually develop life-threatening infectious complications as a result of the loss of their immunity, although the hematologic diseases remain cured. Therefore, it becomes more important to manage infections adequately, especially if they can be prevented in advance. In addition, several outbreaks of measles have been documented around the world [5,6], and severe or fatal measles infections have been reported in HSCT recipients [7,8]. Previous reports have demonstrated the safety and efficacy of immunization against VPDs such as measles, rubella, mumps, and varicella zoster virus (VZV) in pediatric HSCT recipients [9–11]; however, few studies have evaluated the seropositivity for VPDs and safety of live attenuated vaccines in adult HSCT recipients. In addition to HSCT, the emergence of new, more effective therapies, such as molecular-targeted therapy and cancer immunotherapy, has increasingly benefited patients with hematologic malignancies. However, it is still unknown whether immunization against VPDs is needed for patients who receive the newly developed innovative treatments. In

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* Correspondence and reprint requests: Toshihiro Miyamoto, MD, PhD, Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
E-mail address: toshmiya@intmed1.med.kyushu-u.ac.jp (T. Miyamoto).

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this study, we first aimed to evaluate the titers of antibodies against measles, rubella, mumps, and VZV in adult patients who received allogeneic HSCT (allo-HSCT), autologous HSCT (auto-HSCT), or chemotherapy in combination with or without rituximab or bendamustine. Second, we evaluated the safety of live attenuated vaccines and the responses to the vaccines by measuring the titers of antibodies against these viruses following vaccination in seronegative adult HSCT recipients.

PATIENTS AND METHODS

Patients

We comprehensively reviewed the clinical charts of patients with hematologic malignancies who underwent serologic screening for measles, rubella, mumps, and VZV following chemotherapy or HSCT at 4 transplantation centers belonging to the Fukuoka Blood and Marrow Transplantation Groups, including Harasanshin Hospital, Hamanomachi Hospital, Kyusyu Medical Center, and Kyushu University Hospital. The screening tests were performed at the discretion of the physician or at the request of the patient. We subdivided the patients into 3 groups; the chemotherapy group (n = 93) was defined as patients who did not receive either allo-HSCT or auto-HSCT, the allo-HSCT group (n = 74) as patients who received allo-HSCT, and the auto-HSCT group (n = 39) as patients who received auto-HSCT but not allo-HSCT (Table 1). This study was approved by the Institutional Review Board of Harasanshin Hospital (UMIN000016500).

Serologic Measurements of Titers of Antibodies against VPDs

Immunoglobulin G (IgG) antibody titers against measles, rubella, mumps, and VZV were measured by enzyme immunoassay (EIA). EIA was performed by BML (Tokyo, Japan) using a kit from Denka Seiken (Tokyo, Japan). Clinical data, including underlying diseases, history of treatment, and clinical manifestations of VZV infection, were obtained from patient surveys in addition to a comprehensive review of medical records. Based on the recommendations of the Japan Society for Hematopoietic Cell Transplantation [12], a seropositive titer was defined as a titer ≥8.0 for measles and rubella and ≥6.0 for mumps and VZV.

Patients and Criteria for Vaccination

In seronegative HSCT recipients who received live attenuated vaccines, including the measles and rubella (MR) vaccine for preventing measles and rubella (MEARUBIK; Research Foundation for Microbial Disease of Osaka University, Osaka, Japan), the mumps vaccine (Takeda; Takeda Pharmaceutical Company,Tokyo, Japan), and the VZV vaccine (Biken; Research Foundation for Microbial Disease of Osaka University), 2 consecutive doses of live attenuated vaccine were given to HSCT recipients (1) when they were at least 24 and 12 months past allo-HSCT and auto-HSCT, respectively; (2) when they were free from active chronic graft-versus-host disease (GVHD) and no longer received immunosuppressants; (3) when they had not been receiving any transfusions or intravenous immunoglobulin for >3 months and high-dose intravenous immunoglobulin for >6 months; and (4) when they exhibited IgG levels of >500 mg/dL. The second vaccination was performed at least 30 days after the first vaccination. The titers of antibodies that were seronegative before vaccination were measured again at least 4 to 12 weeks after the second vaccination.

Statistical Analysis

The median titers of IgG antibodies against measles, rubella, mumps, and VZV were compared among the 3 groups by the Kruskal-Wallis test. The median titers of IgG antibodies against these VPDs were compared across these groups by the post hoc test. In seronegative patients who received live attenuated vaccine, the titers of antibodies before and after vaccination were compared by the Wilcoxon rank-sum test. Differences in categorical variables between seropositive and seronegative patients after vaccination were analyzed by the Fisher exact test. Multivariate models for seropositive titers of antibodies after vaccination were built using a logistic regression model. EZR (version 2.14.1) was used for statistical analyses [13]. IgG antibody titers of ≥128 and ≤2 were regarded as the upper and lower limits, respectively, in this study. Categorical variables were analyzed by the Fisher exact test. *P* values ≤.05 were considered to indicate statistical significance.

Table 1
Patient Characteristics

	Total (n=206)	Allo-HSCT (n=74)	Auto-HSCT (n=39)	Chemotherapy (n=93)	p value
Median age, years (range)	58 (17-84)	48 (17-73)	60 (26-71)	62 (21-84)	<0.001
Male / Female	98 / 108	28 / 46	23 / 16	47 / 46	0.0565
Disease, n (%)					
AML, MDS	48 (23.3%)	32 (43.2%)	4 (10.2%)	12 (12.9%)	<0.001
ALL	14 (6.7%)	10 (13.5%)	0 (0%)	4 (4.3%)	0.0027
CML, MPN	7 (3.3%)	7 (9.4%)	0 (0%)	0 (0%)	0.0028
ML	101 (49%)	18 (24.3%)	15 (38.4%)	67 (72%)	<0.001
Subtype					
B-cell lymphoma, n (%)	72 (34.9%)	6 (8.1%)	12 (30.7%)	54 (58%)	<0.001
Rituximab, Yes / No, n (%)	68 (33%) / 4 (1.9%)	6 (8.1%) / 0 (0%)	9 (23%) / 3 (7.7%)	53 (56.9%) / 1 (1%)	<0.001
Bendamustine, Yes / No, n (%)	8 (3.8%) / 64 (31.1%)	0 (0%) / 6 (8.1%)	1 (2.5%) / 11 (28.2%)	7 (7.5%) / 47 (50.5%)	<0.001
NK/T-cell lymphoma, n (%)	18 (8.7%)	11 (14.8%)	2 (5.1%)	6 (6.4%)	0.00442
HL	11 (5.3%)	1 (1.3%)	1 (2.5%)	9 (9.7%)	0.0481
Others*, n (%)	36 (17.4%)	7 (9.4%)	20 (51.2%)	9 (9.6%)	0.216
Median days from final therapy to Ab test, days (range)	1,274 (34-9,683)	1,589 (168-9,683)	2,311 (387-7,057)	957 (34-4,317)	<0.001
VZV infection/reactivation, n (%)	37 (17.9%)	22 (29.7%)	7 (17.9%)	8 (8.6%)	0.00237
IgG (mg/dl) at Ab test, median (range)	980 (297-6,255)	1,055 (297-2,056)	882 (443-6,255)	980 (399-2,542)	0.5232
Seropositeve rate, n(%)					
Measles	103 (50%)	15 (20.2%)	15 (38.4%)	73 (78.4%)	<0.001
Rubella	105 (50.9%)	27 (36.4%)	23 (58.9%)	55 (59.1%)	0.071
Mumps	37 (17.9%)	4 (5.4%)	4 (10.2%)	29 (31.1%)	<0.001
VZV	147 (71.3%)	41 (55.4%)	24 (61.5%)	82 (88.1%)	<0.001

Abbreviation
AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; MPN, myeloproliferative neoplasm; ML, malignant lymphoma; HL, Hodgkin lymphoma; Ab, antibody
*Others include 29 patients with multiple myeloma and its related disease, and 7 with aplastic anemia

RESULTS

Patient Characteristics

Patient characteristics are summarized in Table 1. The study enrolled 206 adult Japanese patients. The median ages of patients in the allo-HSCT group, the auto-HSCT group, and the chemotherapy group were significantly different (48 versus 60 versus 62 years; $P < .001$). The underlying diseases of the patients included acute myelogenous leukemia and myelodysplastic syndrome (48 patients), acute lymphocytic leukemia (14 patients), chronic myelogenous leukemia and myeloproliferative neoplasm (7 patients), malignant lymphoma (101 patients), and others including multiple myeloma and its related disorders (29 patients) and aplastic anemia (7 patients). Of 72 patients with B cell lymphoma, 68 were treated with rituximab and 8 were treated with bendamustine. The median number of days from final treatment to testing the titers of antibodies against viruses was significantly greater in the allo-HSCT group (1589 days; range, 168 to 9683 days) and the auto-HSCT group (2311 days; range, 387 to 7057 days) than in chemotherapy group (957 days; range, 34 to 4317 days) ($P < .001$). The incidence of VZV reactivation was higher in the allo-HSCT group (29.7%) and the auto-HSCT group (17.9%) than in the chemotherapy group (8.6%) ($P = .00237$). The levels of IgG in the test of titers against viruses were comparable among the 3 groups (1055 versus 882 versus 980 mg/dL, respectively) ($P = .523$).

Comparison of IgG Antibody Titers

To identify the patient candidates for vaccination, we measured the titers of antibodies against measles, rubella, mumps, and VZV in the allo-HSCT, auto-HSCT, and chemotherapy groups. Table 1 demonstrates the seropositive rates for 4 viruses in the allo-HSCT, auto-HSCT, and chemotherapy groups. The seropositive rates for measles, mumps, and VZV in the allo-HSCT and auto-HSCT groups were significantly lower than those in the chemotherapy group ($P < .001$) (Table 1). Similarly, the allo-HSCT and auto-HSCT groups had a tendency toward a low seropositive rate for rubella compared with the chemotherapy group ($P = .071$).

Figure 1 shows the titers of IgG antibodies against measles, rubella, mumps, and VZV for each patient group before vaccination. The median antibody titers for measles (Figure 1a) and mumps (Figure 1c) in the allo-HSCT and auto-HSCT groups were significantly lower than those in the chemotherapy group. Similarly, the median antibody titers against VZV in the allo-HSCT group were significantly lower than those in the chemotherapy group ($P < .0001$), and the auto-HSCT recipients showed a tendency toward a low titer compared with patients receiving chemotherapy ($P = .077$). In contrast, we found no significant differences in antibody titers against rubella among these 3 groups (Figure 1b), although there was also a tendency toward a lower titer in the allo-HSCT group than that in the

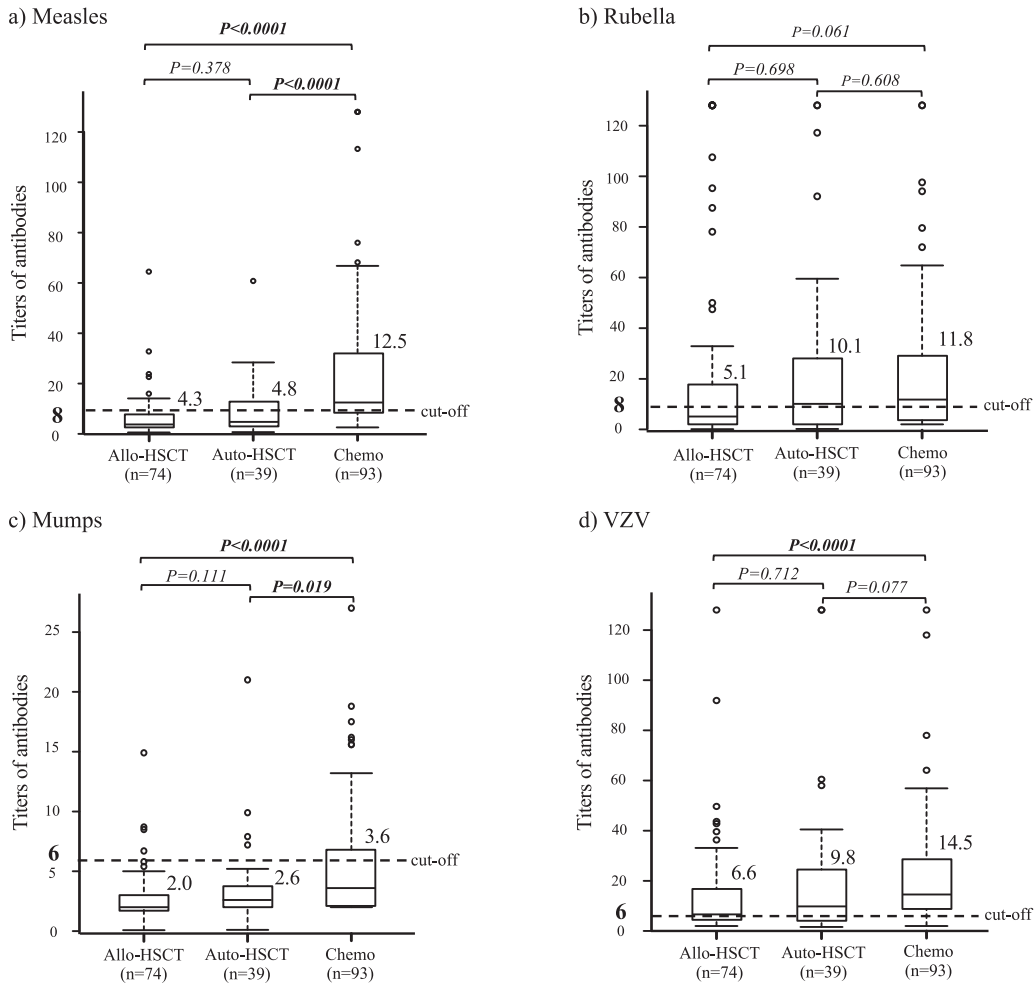

Figure 1. Titers of antibodies against vaccine-preventable diseases in the allo-HSCT, auto-HSCT, and chemotherapy groups. IgG index values ≥8 for measles (a) and rubella (b) and ≥6 for mumps (c) and VZV (d) were considered positive. Allo-HSCT indicates allogeneic hematopoietic stem cell transplantation; auto-HSCT, autologous hematopoietic stem cell transplantation; VZV, varicella zoster virus.

chemotherapy group ($P = .061$). There were no significant differences in antibody titers against these 4 viruses among the allo-HSCT and the auto-HSCT groups (Figure 1).

Next, we investigated the relationship between the titers of antibodies against the 4 viruses and the duration from final chemotherapy or HSCT to the time at measurement of the titer. Of note, in the allo-HSCT group, we found a significant inverse relationship between the antibody titer for measles and the duration from final treatment to measurement of the titer ($r = -0.287$, $P = .015$), but there were no such relationships for the other viruses, rubella ($P = .76$), mumps ($P = .88$), and VZV ($P = .89$) (Figure 2a). In the auto-HSCT group, there were no significant relationships between antibody titers for the 4 viruses and duration from final treatment to measurement of the titer (Figure 2b). In the chemotherapy group, we found significant inverse relationships between antibody titers and the duration from final treatment to measurement of the titer for mumps ($r = -0.278$, $P = .015$) and VZV ($r = -0.264$, $P = .0152$) (Figure 2c).

Because rituximab can deplete B lineage cells that produce IgG, we examined the influence of rituximab on antibody titers against viruses in 67 patients with lymphoma, including B cell, NK/T cell, and Hodgkin lymphoma, who received chemotherapy but not HSCT. Unexpectedly, the median antibody titer against measles was significantly higher in 53 patients who received rituximab than in 14 patients who did not receive rituximab (17.4 versus 8.1, $P = .0101$) (data not shown). However, there were no significant differences between patients with and without rituximab in antibody titers against other viruses, such as rubella (17.4 versus 9.7, $P = .297$), mumps (3.6 versus 2.75, $P = .278$), and VZV (15.25 versus 24.2, $P = .393$), among the patients with and without rituximab (data not shown). Similarly, we tested the effect of bendamustine on antibody titers against viruses in 7 patients with lymphoma treated with bendamustine compared with 60 patients with lymphoma treated without this drug. There were no significant differences in antibody titers against measles (18.5 versus 14.85, $P = .532$), rubella (3.8 versus 3.6, $P = .90$), mumps (4.6 versus 14.0, $P = .172$), and VZV (18.5 versus 14.8, $P = .532$) between these 2 groups (data not shown).

Factors Associated with Seropositivity in Serologic Screening

We evaluated the relationships between the rate of seropositivity for these 4 viruses and several factors, such as age, underlying disease, level of IgG, prior rituximab therapy, acute GVHD, chronic GVHD, and others, among the 3 patient groups (Table 2). Interestingly, we found a significant association between previous rituximab therapy and the rate of seropositivity for measles in the chemotherapy group ($P = .009$) (Table 2). In the allo-HSCT group, univariate analysis showed close associations between a history of chronic GVHD and seropositivity for measles ($P = .0059$) and between treatment for chronic GVHD and seropositivity for measles ($P < .001$) and rubella ($P = .0077$).

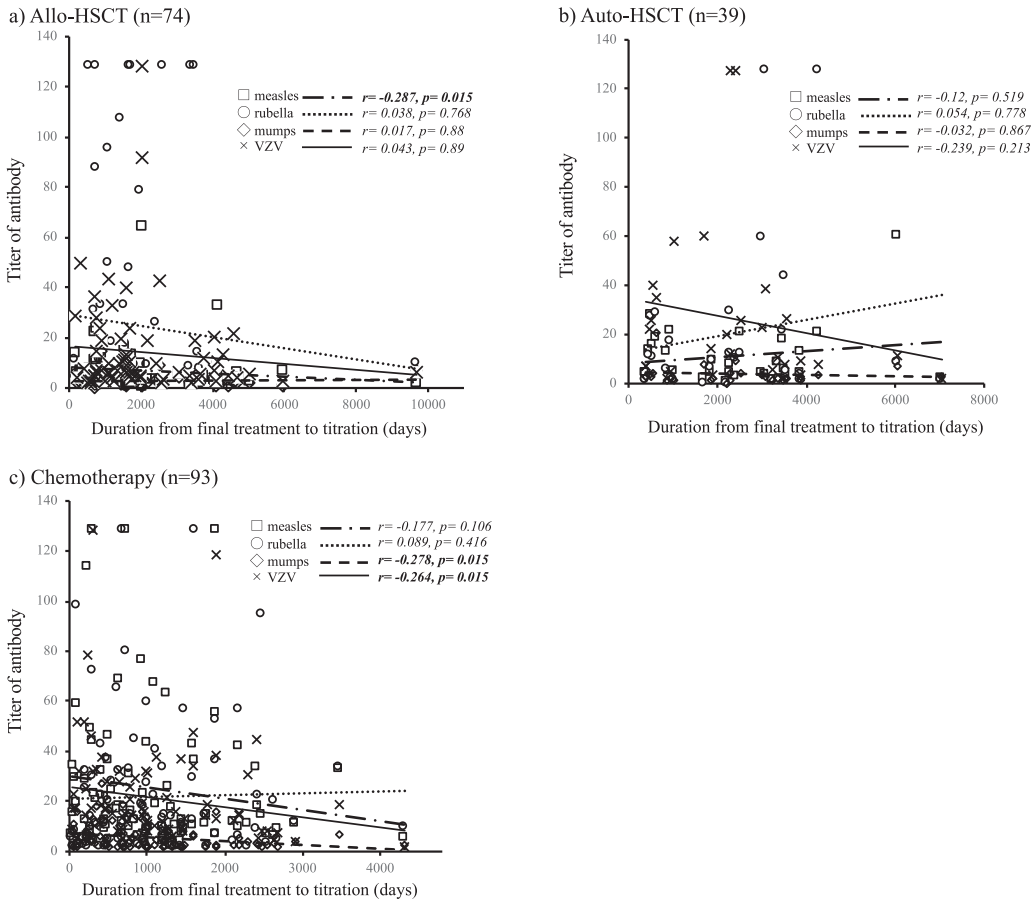

Figure 2. Correlations between antibody titers and the duration from final therapy to measurement of titers in the allo-HSCT (a), auto-HSCT (b), and chemotherapy (c) groups. Squares, circles, diamonds, and crosses indicate titers for measles, rubella, mumps, and VZV in each individual, respectively. Lines indicate the relation between titer and the duration from final treatment to titration: dash-dotted line for measles, dotted line for rubella, dashed line for mumps, and solid line for VZV. Allo-HSCT indicates allogeneic hematopoietic stem cell transplantation; auto-HSCT, autologous hematopoietic stem cell transplantation; VZV, varicella zoster virus.

Table 2
Univariate Analysis for Seropositivity at Serologic Antibody Screening

Factor	Allo-HSCT (p value)				Auto-HSCT (p value)				Chemotherapy (p value)			
	measles	rubella	mumps	VZV	measles	rubella	mumps	VZV	measles	rubella	mumps	VZV
Age < vs ≧50 y	0.563	1	0.614	0.474	0.396	1	0.141	0.678	0.378	0.129	0.437	1
Female vs Male	0.785	0.453	0.62	0.462	0.318	0.342	1	0.342	1	0.403	1	0.197
Lymphoid vs myeloid malignancy	0.385	0.338	0.62	0.0947	0.631	1	1	0.631	0.178	0.775	0.768	1
IgG < vs ≧1000	1	0.578	0.48	0.407	0.442	0.454	0.611	1	0.331	1	0.0543	1
Prior rituximab therapy, Yes vs No	0.187	0.465	1	0.289	0.266	0.056	0.556	0.262	***0.009***	0.14	0.652	1
Acute GVHD + vs -	0.093	0.757	0.102	0.351	NA	NA	NA	NA	NA	NA	NA	NA
Acute GVHD Ⅲ/Ⅳ + vs -	1	0.636	1	1	NA	NA	NA	NA	NA	NA	NA	NA
Treatment for acute GVHD, Yes vs No	0.44	0.397	1	1	NA	NA	NA	NA	NA	NA	NA	NA
Chronic GVHD + vs -	***0.0059****	0.627	1	0.227	NA	NA	NA	NA	NA	NA	NA	NA
Treatment for chronic GVHD, Yes vs No	***<0.001****	***0.0077****	0.618	0.284	NA	NA	NA	NA	NA	NA	NA	NA
Months from final therapy to titration <68 vs ≧68 mon	0.139	0.806	0.632	0.467	0.274	0.471	1	1	1	1	0.0527	0.0624

*Bold numerics indicate statistically significance.

Next, we verified the relationships between these factors and the serostatus by multivariate analysis. The analysis showed that a history of chronic GVHD was significantly associated with seropositivity for measles (odds ratio, 0.05; 95% confidence interval [CI], 0.00 to 0.61; $P = .019$) (Table 3), but no association with treatment of chronic GVHD was documented. Multivariate analysis found no correlation between previous rituximab therapy and seropositivity for any viruses in the 3 patient groups.

Vaccinations

Following the guidelines of the Japan Society for Hematopoietic Cell Transplantation (JSHCT) [12], 37 seronegative HSCT recipients received the live attenuated vaccines. Patient characteristics are shown in Table 4. The median age at receiving the vaccines was 46 years (range, 17 to 73 years). The median duration from HSCT to antibody titration was 69.3 months (range, 25.8 to 212.6 months). Twenty-nine of 37 patients received allo-HSCT, and 8 received auto-HSCT. Among the allo-HSCT recipients, 7 patients received a related bone marrow graft, 11 received an unrelated bone marrow graft, 3 received related peripheral blood stem cells, and 8 received cord blood stem cells. Of 29 allo-HSCT recipients, 2 patients had developed grade Ⅲ to Ⅳ acute GVHD, and 7 had a history of chronic GVHD (limited in 4 patients and extensive in 3 patients). MR vaccine was administered to 26 allo-HSCT recipients and 7 auto-HSCT recipients. In contrast, mumps vaccine was administered to 8 allo-HSCT recipients and 3 auto-HSCT recipients, and VZV vaccine was administered to 4 allo-HSCT recipients and 1 auto-HSCT recipient.

Safety of Live Attenuated Vaccines

In this study, we found no infectious adverse events associated with live attenuated vaccines in any patients who received the vaccination. Three of 37 recipients (8.1%) developed mild symptoms after vaccination. One patient developed

Table 3
Multivariate Analysis for Seropositivity

Analysis	Factor	Odds ratio	95% CI	p value
Seropositivity for measles at screening	Chronic GVHD - vs +	0.05	0.00-0.61	*0.019**
	Lymphoid vs myeloid malignancy	2.26	0.50-7.42	0.43
	Prior ritximab therapy, Yes vs No	0.48	0.02-9.54	0.63
Seropositivity for viruses after vaccination	Chronic GVHD - vs +	0.06	0.01-0.68	*0.023**
	Lymphoid vs myeloid malignancy	1.19	0.2-7.05	0.79
	Prior ritximab therapy, Yes vs No	0.19	0.01-2.52	0.21

*Bold numerics indicate statistically significance.

Table 4
Characteristics of 37 HSCT Recipients Who Received Vaccines

Characteristics	No. of patients
Age at HSCT, median (range)	43 (10-69)
Age at vaccinations, median (range)	46 (17-73)
Months from HSCT to Ab test, median (range)	69.3 (25.8 - 212.6)
Male / Female	13 / 24
Disease, n (%)	
AML, MDS	10 (27%)
ALL	6 (16.2%)
CML, MPN	2 (5.4%)
MM, MM-related disease	5 (13.5%)
ML	9 (24.3%)
AA	5 (13.5%)
Type of HSCT, n (%)	
Autologous	8 (21.6%)
Allogeneic	29 (78.3%)
R-BMT	7 (18.9%)
UR-BMT	11 (29.7%)
R-PBSCT	3 (8.1%)
CBT	8 (21.6%)
History of acute GVHD (n=29)	
none	10 (27%)
Grade I - II	17 (47.9%)
Grade III-IV	2 (5.4%)
History of chronic GVHD (n=29)	
none	22 (59.4%)
limited	4 (10.8%)
extensive	3 (8.1%)
History of VZV, n (%)	16 (43.2%)
IgG value (mg/dl), median (range)	1,107 (443-2143)
Prior rituximab therapy, n (%)	5 (13.5%)
Vaccinations	
MR for measles (Allo / Auto), n=32	25 (67.5%) / 7 (18.9%)
MR for rubella (Allo / Auto), n=20	16 (43.2%) / 4 (10.8%)
Mumps (Allo / Auto), n=11	8 (21.6%) / 3 (8.1%)
VZV (Allo / Auto), n=6	5 (13.5%) / 1 (2.7%)

Abbreviation

AA, aplastic anemia; R-BMT, bone marrow transplantation from related donor;

UR-BMT, bone marrow transplantation from unrelated donor;

PBSCT, peripheral blood stem cell transplantation; CBT, cord blood transplantation

lymphadenopathy and sore throat after MR vaccine, which resolved without specific treatments. Fever and mild skin eruption were observed in the other 2 patients. No severe adverse events were observed.

Response to Live Attenuated Vaccines

To evaluate seroconversion following vaccination, we measured the titers of antibodies against for viruses (measles, rubella, mumps, and VZV) before and after vaccination. Titers of antibodies before and after vaccination were obtained in 36 of 37 HSCT recipients who received the vaccination. Among these, 32 received MR vaccine; 20 were seronegative for both measles and rubella, whereas 12 were seronegative only for measles. Mumps and VZV vaccines were administered to 11 and 6 seronegative patients, respectively.

After vaccination, there were significant increases in the titers of antibodies against measles ($P < .001$), rubella ($P = .0412$), and mumps ($P = .0137$) but not VZV ($P = .0938$) (Figure 3). Of note, 6 of 32 patients (18%) who were seronegative for measles after vaccination became seropositive after MR vaccination. Similarly, 6 of 20 patients (30%), 3 of 11 patients (27%), and 3 of 6 patients (50%) who were seronegative for rubella, mumps, or VZV, respectively, became seropositive after vaccination (Figure 3).

Factors Associated with Seroconversion after Vaccination

To identify the factors associated with seroconversion following vaccination, we evaluated the effects of several factors, such as age, acute GVHD, chronic GVHD, underlying disease, prior rituximab therapy, and type of HSCT on seroconversion (Table 5). Of note, univariate analysis showed that only a history of chronic GVHD was associated with seroconversion after vaccination ($P = .0365$).

Next, we again verified the relationship between these factors and seroconversion rates following vaccination by multivariate analysis, excluding 8 patients in the auto-HSCT group from the analysis. Multivariate analysis showed that only a history of chronic GVHD was significantly associated with seroconversion (odds ratio, 0.06; 95% CI, 0.01 to 0.68; $P = .023$) (Table 3).

DISCUSSION

There are few data about the immune status of HSCT recipients against VPDs, especially for adult recipients. Therefore, we

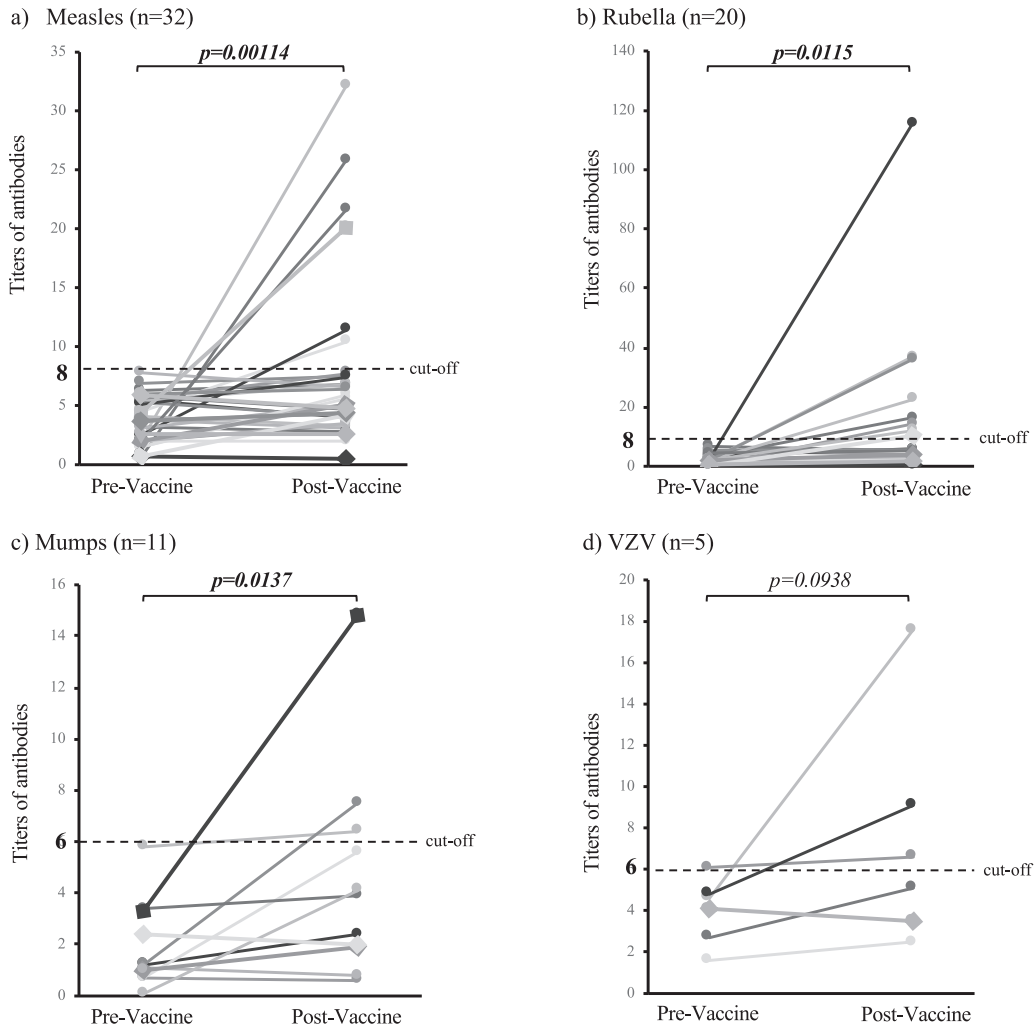

Figure 3. Comparison of antibody titers for measles (a), rubella (b), mumps (c), and VZV (d) before and after vaccination. Squares and circles indicate titers in auto-HSCT and allo-HSCT recipients, respectively. Allo-HSCT indicates allogeneic hematopoietic stem cell transplantation; auto-HSCT, autologous hematopoietic stem cell transplantation; VZV, varicella zoster virus.

Table 5
Univariate Analysis for Seroconversion after Vaccination

Factor	Seropositive (n=17)	Seronegative (n=19)	p value
Age < vs ≧ 50 y	7 / 10	12 / 7	*0.316*
Female vs Male	9 / 8	14 / 5	*0.299*
Lymphoid vs myeloid malignancy	10 / 7	10 / 9	*0.749*
IgG < vs ≧ 1000	4 / 7**	5 / 11**	*1*
Prior ritximab therapy, Yes vs No	4 / 13	1 / 18	*0.167*
Allo-HSCT vs Auto-HSCT	12 / 5	16 /3	*0.434*
Acute GVHD + vs -	8 / 9	9 / 10	*1*
Acute GVHD III/IV + vs -	0 / 17	2 / 17	*0.487*
Treatment for acute GVHD, Yes vs No	4 / 13	5 / 14	*1*
Chronic GVHD + vs -	6 / 11	1 / 18	***0.036****
Treatment for chronic GVHD, Yes vs No	1 / 16	1 / 18	*1*
Months from final therapy to titration <68 vs ≧68 mon	8/9	12 / 7	*0.506*

*Bold numerics indicate statistically significance.

** Some data about IgG level were missing

checked the serostatus of adult HSCT patients against measles, rubella, mumps, and VZV in comparison with the patients receiving chemotherapy. In 2005, Shiraishi et al. [14] epidemiologically investigated the rates of seropositivity against these viruses in 686 healthy Japanese adults ages 20 to 60 years. The rate of seropositivity was 91.4% for measles, 90.1% for rubella, 84.8% for mumps, and 99.3% for VZV. In our 74 allo-HSCT recipients, the rate of seropositivity was 20.2% for measles, 36.4% for rubella, 5.4% for mumps, and 55.4% for VZV. These rates were much lower than those in healthy adults, as well as in patients receiving chemotherapy. Our data are also consistent with those of the previous study of adult Japanese allo-HSCT recipients by Kawamura et al. [15]. They reported that the seropositive rate following allo-HSCT was <44% for measles, <36% for rubella, and <10% for mumps [15] (Table 6). These data indicate that adult HSCT recipients are highly recommended to receive vaccination against VPDs.

To identify factors influencing seropositivity at screening as well as seroconversion rates following vaccination, we evaluated their association with several factors in adult patients. Surprisingly, in serologic screening, a history of chronic GVHD was significantly associated with seropositivity for measles. Furthermore, following vaccination, the seroconversion rate was also significantly associated with a history of chronic GVHD, despite the small number of cases (n = 7). Our results in adult HSCT recipients are contrary to the previous reports of pediatric HSCT recipients [4, 16]. In this study, all patients underwent antibody examination after GVHD resolved completely if they had discontinued immunosuppressants. Thus, their cellular and humoral immunity, including memory B cells, might have been sufficiently restored to the extent of producing antibodies against VPDs. In addition, numerous studies have shown a close association between chronic GVHD and relapse-free survival from leukemia, suggesting that chronic GVHD might induce a graft-versus-leukemia effect via allogeneic immunity [17]. In patients with chronic GVHD, aberrant T and B cell activation might generate antibody-secreting cells that produce alloantibodies to polymorphic recipient antigens [18]. Thus, following vaccination in patients with a history of chronic GVHD, such pathogenetic mechanisms might be evoked again by recognition of xenogeneic viral pathogens, which could augment the immune response against VPDs, resulting in a high seroconversion rate, although the precise mechanisms remain unknown. Nevertheless, the seroconversion rate varied among vaccines in this study. Higher seroconversion was documented for measles in the HSCT recipients with a history of cGVHD, which might be partially caused by the inherent antigenic differences among the individual vaccines despite the small number of cases. Therefore, it is also necessary to verify this finding in a larger number of HSCT recipients.

Theoretically, once seropositivity against viruses has been acquired after primary or latent infection or vaccination, the antibody titers can gradually decrease with age, accompanied by a decline in immunity [19,20]. Davidkin et al. [21] clearly demonstrated that titers of antibodies against measles, rubella, and mumps significantly declined with years after vaccination in a 20-year follow-up of healthy pediatric individuals. Thus, the rate of seropositivity and antibody titers against viruses in pediatric allo-HSCT recipients would be higher than those in adult recipients [19,20,22], although they might depend on the time when these patients were infected with these viruses

Table 6
Seropositive Rate against Measles, Rubella, and Mumps in Allo-HSCT Recipients

Author	Year	Patient No.	Median age at Ab test (range)	Department	Median duration form allo-HSCT to Ab test (range)	Seropositive rate (%)		
						Measles	Rubella	Mumps
Ljungman [24]	1989	57	NA*	Pediatrics	> 2 years	51%	76%	42%
Inaba [20]	2012	210	9.5 y (1.6-25.1)	Pediatrics	annually	30%	44.4%	29.7%
Ljungman [21]	1994	124	NA*	Pediatrics	annually	47%	47%	37%
Machado [25]	2005	51	25 y (6-55)	Pediatrics & Adult	1 year (0.7-1.5)	82.8%	-	-
Ljungman [26]	2004	395	27.7 y (1-63)	Pediatrics & Adult	> 2 years	64%	-	-
Spoulou [27]	2004	30	12.5 y (2-22.8)	Pediatrics	2.1 years (2-19)	13.3%	33.3%	66.6%
Patel [23]	2007	38	13 y (3.7-18.7)	Pediatrics	1.6 years (1.4-3.2)	60%	-	-
Kawamura [16]	2014	45	31 y (16-65)	Adult	2.2 years (2.1-5.6)	<44%	<36%	<10%
Our study	2018	74	48 y (17-73)	Adult	5.3 years (0.4-26.5)	20.2%	36.4%	5.4%

*NA, not available

or vaccinated. Table 6 summarizes previous reports of seropositivity for measles, rubella, and mumps in pediatric and/or adult allo-HSCT recipients. As expected, pediatric allo-HSCT recipients have higher seropositive rates than adult recipients [19,20,22–26]. In the present study, we also found a significant inverse association between titers of antibodies against several viruses and the duration from final chemotherapy or HSCT to the time at the measurement of the titer. Thus, aging may be one of the important factors for seronegative or low titers against viruses, and therefore, it would be crucial for elderly patients to receive vaccination at the earliest possible opportunity following allo-HSCT. In addition, our study, which revealed that allo-HSCT strongly suppressed humoral immunity over time, emphasizes the necessity of vaccination for all adult allo-HSCT recipients, even if they are seropositive after allo-HSCT.

Despite the recommendations of several guidelines for vaccination of HSCT patients against VPDs [2,3,27], these vaccinations are not routinely performed, at least in Japan, because of the paucity of information about the safety of live attenuated vaccines. In this study, 3 of 37 HSCT recipients (8.1%) experienced mild adverse events following vaccination, which quickly resolved without any treatment. These results support the safety of administering the live attenuated vaccine, at least against measles, rubella, mumps, and VZV, for adult HSCT recipients. In addition, the titers of antibodies significantly increased after vaccination for measles, rubella, and mumps, although the rates of seroconversion after vaccination were relatively low (19% for measles, 30% for rubella, 27% for mumps) compared with the findings of previous studies in pediatric HSCT patients [20]. An effective vaccine response in the elderly is reportedly often hampered by immunologic aging [19]. However, the interpretation of titers of antibodies after vaccination remains controversial. For example, of 14 pediatric HSCT recipients receiving vaccination, 7 patients did not attain seropositivity but possessed cellular immunity against VPDs, indicating the presence of a dichotomy between the humoral and the cell-mediated response in HSCT recipients [28]. These observations suggest that seronegative titers of antibodies do not always indicate a lack of protection against viral infection. To evaluate the need for further vaccinations in seronegative adult HSCT recipients after 2 shots of vaccines, reassessment of immune reconstitution, including cell-mediated immunity, such as total and $CD4^+$ T cell subsets and T cell proliferative response, would be needed [29]. In addition, we have not verified the efficacy of vaccination, which could expectedly prevent the viral infectious diseases. Therefore, long-term observational studies are also warranted to evaluate the efficacy of vaccinations in HSCT recipients.

In contrast to HSCT recipients, there has been no guideline recommending vaccination for patients receiving chemotherapy. Because data are lacking on the titers of antibodies against VPDs, as well as the incidence of VPDs, in patients receiving chemotherapy, it remains unknown whether vaccination against VPDs is needed for such patients. In the present study, we showed that the titers of antibodies against measles, rubella, and VZV were higher in the chemotherapy group than in HSCT recipients. In the HSCT recipients, conditioning regimens followed by immunosuppressants as well as subsequent reconstitution of the donor-derived immune system could induce an extremely profound immune suppression compared with the patients receiving chemotherapy. Of note, we found no significant differences in titers of antibodies between patients receiving chemotherapy with or without rituximab or bendamustine. Rituximab is supposed to have a negative impact on immune status by depleting B lymphocytes, which increases the risk of developing reactivation of hepatitis B virus or cytomegalovirus [30]. Similarly, bendamustine frequently induces lymphopenia [31], resulting in a high incidence of viral infectious complications. A multicenter retrospective analysis of a cohort of 234 patients treated with a bendamustine-containing regimen reported that 26 patients (11.5%) developed

viral infections [32]. In our study, the number of patients treated with rituximab or bendamustine was too small to enable a conclusion about the effects of these drugs. A larger prospective study is needed to clarify the need for vaccination, especially for patients receiving numerous upcoming innovative novel agents such as molecular-targeted therapy and cancer immunotherapy, in the near future.

In summary, adult HSCT recipients lost their immunity to VPDs compared with patients receiving chemotherapy. Despite the small number of cases, the results showed that the live attenuated vaccines were safely administered to HSCT recipients. However, the seropositive rates after vaccinations were lower than those in the previously reported studies of pediatric HSCT recipients. A further long-range observational study combined with evaluation of cell-mediated immunity is needed to evaluate the efficacy of vaccination in seronegative patients after vaccinations.

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