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RAPID COMMUNICATION

Antibody response to COVID-19 vaccine in 130 recipients of hematopoietic stem cell transplantation

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Abstract

We evaluated anti-spike protein antibody (anti-S) production in 130 hematopoietic stem cell transplant (HSCT) recipients who received the coronavirus disease-2019 vaccine. Sixty-five received allo-HSCT and 65 received auto-HSCT. Disease-specific treatments were being administered to 43.1% of allo-HSCT and 69.2% of auto-HSCT patients. Seropositivity was observed in 87.7% of allo-HSCT and 89.2% in auto-HSCT patients. Anti-S antibody production was significantly impaired in auto-HSCT patients compared with controls (178U/mL [0.4–4990.0] vs. 669 U/mL [40.3–4377.0], $p < 0.001$), but not in allo-HSCT patients (900 U/mL [0.4–12,893.0] vs. 860 U/mL [40.3–8988.0], $P = 0.659$). Clinically relevant anti-S antibody levels (> 264 U/mL) were achieved in 59.2% of patients (76.9% in allo-HSCT and 41.5% in auto-HSCT). The main factors influencing the protective level of the antibody response were the CD19 + cell count and serum immunoglobulin G levels, and these were significant in both allo-HSCT and auto-HSCT patients. Other factors included time since HSCT, complete remission status, use of immunosuppressive drugs, and levels of lymphocyte subsets including CD4, CD8 and CD56 positive cells, but these were only significant in allo-HSCT patients. Allo-HSCT patients had a relatively favorable antibody response, while auto-HSCT patients had poorer results.

Keywords COVID-19 vaccine · Antibody · Allogeneic HSCT · Autologous HSCT

Introduction

Patients who have undergone hematopoietic stem cell transplantation (HSCT) are at high risk of severe acute respiratory syndrome-coronavirus-2 (SARS-Cov-2) infection and have a poorer prognosis [1, 2]. Vaccination is expected to prevent and reduce the severity of coronavirus disease-2019 (COVID-19), but the actual clinical efficacy of vaccination in HSCT patients remains unclear. Antibody titer after vaccination is considered to be one of the most important indicators for infection prevention [3], but it is difficult to evaluate due to various immune responses toward vaccination among post-transplant patients. This study evaluated the antibody production among HSCT patients who received the COVID-19 vaccine.

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Patients and methods

This study is a prospective observational study of the serologic response to the COVID-19 vaccine in HSCT patients who were being treated or followed-up at Kameda Medical Center, Kamogawa-shi, Japan. All patients who received the COVID-19 vaccine from July 1 to November 10 and were attending our hospital regularly were offered the opportunity to participate in this study. Age matched immunocompetent volunteers ($N = 140$, median age 46 years, range; 24 to 71 years) served as healthy controls (HCs).

All participants completed the 2 vaccine schedule with either the BNT162b2 (Pfizer- BioNTech) or mRNA 1273 vaccine (Moderna). The blood data were obtained approximately three to eight weeks after the second vaccination. Informed consent was obtained from all study participants or their family members. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical review committee of Kameda Medical Center.

The antibody titers to the anti-spike (anti-S) immunoglobulin and anti-nucleocapsid (anti-N) immunoglobulin

of SARS-Cov-2 were measured using the Elecsys Anti-SARS-CoV-2 S assay (Roche, Basel, Switzerland). The cut-off index values for seropositivity were 0.8 U/mL for anti-S antibody and 1.0 U/mL for anti-N antibody (≥ 1.0 as recommended by the manufacturer). According to a previous study, an anti-S antibody titer of ≥ 264 U/mL is considered clinically protective against Sars CoV-2 infection [4–6]. The baseline characteristics were compared using the Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. Two-sided *p* values of < 0.05 were considered statistically significant.

Results and discussion

Table 1 shows the demographics, clinical characteristics, and antibody responses of patients who underwent allogeneic HSTC (allo-HSCT) and autologous HSCT (auto-HSCT). There were no adverse reactions requiring hospitalization or treatment other than antipyretics in the participants of this study.

At the time of vaccination, 28 (43.1%) in allo-HSCT and 45 (69.2%) auto-HSCT patients were receiving active therapy. In brief, among the patients who received allo-HSCT, 18 with GVHD received immunosuppressive treatment using cyclosporine A, tacrolimus, and/or mycophenolate mofetil with or without steroid. Three patients received treatment for relapsed disease. In patients who received auto-HSCT, 45 patients (69%) received treatment for their underlying disease such as myeloma in 41, and B-cell lymphoma in four.

No patients showed anti-N antibody indicating that no one had a previous COVID-19 exposure. Antibody production was observed in 100% of the HCs and 88.5% of the transplant patients; 87.7% (57/65) in allo-HSCT group and 89.2% (58/65) in auto-HSCT group. The percentage of patients with clinically relevant antibody levels was 59.2% (77/130) overall, 76.9% (50/65) in allo-HSCT group, and 41.5% (27/65) in auto-HSCT group. In the COVE trial, a

Table 1 Patient characteristics

Variable	Allo-HSCT patients (*N* = 65)	Auto-HSCT patients (*N* = 65)	*p* value
Age at vaccination, median range	55 yr (23–8 0)	70 yr (34–79)	< 0.001
Sex, Male, *N* (%)	41 (63.1%)	33 (50.8%)	0.215
Covid-19 vaccine, *N* (%)			
mRNA-1273 (Moderna)	2 (3.1%)	1 (1.5%)	0.323
BNT162b2 (Pfizer-BioNTech)	62 (95.4%)	59 (90.8%)	
Time from transplant to vaccination, (months) median range	92 (4–255)	49 (4 -185)	0.003
Underlying disease, *N*	AML (29), MDS (4), CML(1), ALL (15), NHL (9), HL(1), MM (1), AA (5)	NHL (19), HL (2), MM (44)	
Conditioning, *N*	MAC (39), RIC (26)	N/A	
Graft source, *N*	PBSC (29), BM (30), CB (6)	PBSC (65)	
Donor type, *N*	Haplo (15), MRD (16), MUD (10), MMRD (3), MMUD (21)	N/A	
Graft versus host disease, *N* (%)	22 (33.8%)	N/A	
Disease status, *N*	CR (56), not CR (4), Other (5)	CR (55), not CR (10)	0.017
Ongoing treatment, *N* (%)	28 (43.1)	45 (69.2)	
	Steroids (17), TAC (11), CyA (5), MMF (5), Other treatment (14)	Steroids (41), IMiDs (31), PI (11), CD38 monoclonal antibodies (22), Other treatments (7)	
Serum IgG median, mg/dL (range)	1129 (100–2093)	610 (71–1943)	< 0.001
Antibody titer against Covid-19 Vaccine			
Anti-S seropositive (> 0.8 U/mL), *N* (%)	57 (87.7%)	58 (89.2%)	1.000
Anti-S titer,median (U/mL, range)	900 (0.40–12,893.00)	178 (0.40–4990.00)	< 0.001
Anti-S-IgG (> 260U/mL) *N* (%)	50 (76.9%)	27 (41.5%)	< 0.001

AA Aplastic anemia, *AML* Acute myeloid leukemia, *ALL* Acute lymphoblastic leukemia, *BM* Bone marrow, *CB* Cord blood, *CML* Chronic myeloid leukemia, *CR* Complete remission for leukemia and lymphoma, complete response for myeloam, *CyA* Cyclosporine, *GVHD* Graft vs host disease, *HL* Hodgkin's lymphoma, *IMiDs* Immunomodulatory drug, *MAC* Myeloablative conditioning, *MDS* Myelodysplastic syndromes, *MM* Multiple myeloma, *MMF* Mycophenolate mofetil, *Haplo* haploidentical donor, *MRD* matched related donor, *MUD* matched unrelated donor, *MMRD* Mismatched related donor, *MMUD* Mismatched unrelated donor, *MRD* Matched related donor, *MUD* Matched unrelated donor, *MTX* Methotrexate, *NHL* Non Hodgkin lymphoma, *PBSC* Peripheral blood stem cells, *PI* Proteasome inhibitors, *PTCY* post Cyclosphosphamide, *RIC* Reduced intensity conditioning, *TAC* Tacrolimus

bound antibody unit (BAU) of ≥ 250 BAU/mL is associated with ~ 90% mRNA efficacy [7]. Feng et al. reported that the 80% protection level of anti-S antibodies against the alpha variant of SARS-CoV-2 was 264 BAU/mL [4]. However, there is no standardized serological assay for SARS-CoV-2 antibody titers. Recently, Perkmann et al. [5] directly compared the values between assays, and the BAU/mL of anti-SARS-CoV-2 immunoglobulin was the equivalent to that of U/mL used in the Elecsys Anti-SARS-CoV-2 S assay (Roche). Therefore, the protective level of anti-S antibody titer in this study was set to ≥ 264 U/mL. Figure 1 indicates the box-plot of the anti-S antibody levels of patients receiving allo-HSCT, auto-HSCT and HCs. There was no significant difference in antibody titers between allo-HSCT patients and HCs but allo-HSCT patients had significantly higher anti-S antibody titers compared to auto-HSCT patients. Since the auto-HSCT group consisted of patients with lymphoma ($n = 21$) and myeloma ($n = 44$), and the majority of the myeloma patients receive maintenance therapy, we compared the antibody titers of the lymphoma and myeloma patients within the auto-HSCT group (Supplemental Fig. 1A). The median antibody titers were 376 U/mL (36–1462) in the lymphoma group and 151 U/mL (39–434) in the myeloma group, with no statistically significant differences. There was no statistically significant difference in the period between transplantation to vaccination (median: lymphoma 63 months [range; 4–122 months] *vs.* myeloma 47 months [range; 5–185 months] $P = 0.944$). Intriguingly, antibody titer was even higher in patients receiving allo-HSCT who do not have GVHD and did not receive any immunosuppressive treatment. Although serum anti-S antibody production tends to recover with time after transplantation, there are some cases in which serum anti-S antibody does not recover for a long time after transplantation due to the differences in treatment and complications (Supplemental Fig. 2S).

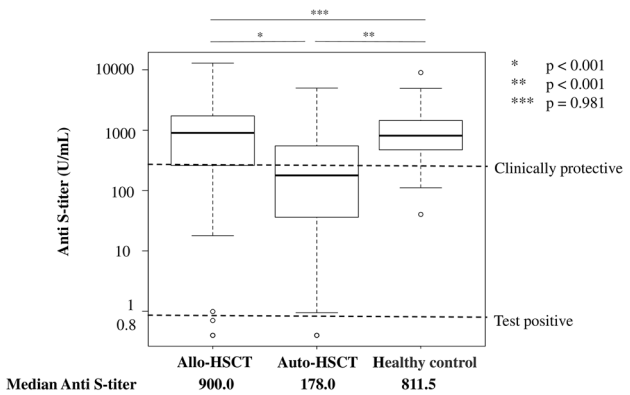

Fig. 1 Box-plot of anti-S antibody titer after allogeneic, autologous HSCT recipient and healthy controls

The factors, contributing to the development of clinical protective antibody titers were examined (Table 2). The CD19 + lymphocyte counts and serum IgG levels were associated with insufficient protective level of antibody production in both allo-HSCT and auto-HSCT patients, whereas post-transplant period, use of immunosuppressive drugs, presence of GVHD, peripheral lymphocyte counts as well as CD4 +, CD8 +, and CD 56 + lymphocyte counts were associated with allo-HSCT patients only. Delayed B-cell quantitative recovery was commonly associated with inadequate antibody production in both allogeneic and autologous HSCT patients. It was also associated with the duration of the post-transplant period and recovery of T-cell subsets in allogeneic HSCT patients because post-transplant treatment aimed to suppress cellular immunity in allo-HSCT. Meanwhile B-cell or plasma cell targeted

Table 2 Factors affecting the achievement clinically relevant antibody titer (anti-S ≥ 264 U/mL)

	Allogeneic HSCT			Autologeous HSCT		
Variable	Anti-S < 264 U/mL	Anti-S ≥ 264 U/mL	*P* value	Anti-S < 264 U/mL	Anti-S ≥ 264 U/mL	*P* value
Number of patients (%)	15 (23.1)	50 (76.9)	NA	38 (58.5)	27 (41.5)	NA
Age, (range)	58 (34–65)	55 (23–80)	0.503	70 (34–79)	72 (46–79)	0.113
Post-transplant period, month(range)	19 (4–167)	109 (6–255)	< 0.001	39 (4–185)	50 (19–122)	0.351
Complete remission/response	10 (67%)	46 (92%)	0.044	31 (82%)	24 (89%)	0.503
Presence of GVHD	40 (80%)	10 (20%)	< 0.001	NA	NA	NA
Use of immunosuppressants, *N* (%)	13 (86.6)	11 (22.0)	< 0.001	0	0	NA
Lymphocyte × 10^3 /μL (range)	0.9 (0.3–2.3)	2.3 (0.9–5.0)	< 0.001	1.2 (0.3–2.2)	1.4 (0.2–4.8)	0.05
CD19 + cells /μL (range)	68 (0–811)	450 (36–1798)	< 0.001	42 (0–510)	189 (26–1379)	0.001
CD4 + cells /μL (range)	239 (72–603)	605 (226–1213)	< 0.001	2889 (119–920)	361 (124–904)	0.23
CD8 + cells /μL (range)	395 (85–934)	499.5 (116–3129)	0.016	575 (138–1205)	529.3 (165–1760)	0.715
CD56 + cells /μL (range)	103 (25–490)	261 (58–1024)	0.002	107 (8–639)	229 (7–828)	0.152
Serum IgG, mg/dL (range)	566 (100–1260)	1191 (117–2093)	< 0.001	463.0 (98–1654)	887 (71–1943)	0.001

HSCT hematopoietic stem cell transplantation, *GVHD* graft versus host disease, *NA* not assessed

therapy after transplant is associated with suppression of humoral immunity in auto-HSCT.

Attolico et al. recently reported the antibody production after vaccination in 62 allo-HSCT and 52 auto-HSCT patients [8]. Seroreactivity to the vaccine was observed in 84% of patients. Antibody titers of auto-HSCT patients were significantly lower than those of HCs and allo-HSCT patients, and there was no difference in antibody titers between allo-HSCT patients compared to HCs.

There have been a number of reports of breakthrough infections associated with a decline in vaccine antibody titers over time [9]. In particular, breakthrough infections caused by the delta and omicron variants have been reported, even in fully vaccinated recipients, and many countries have started to administer a third booster dose [10]. However, there are few reports on the efficacy of the third vaccine booster dose in immunocompromised patients [11], including transplant recipients who have a decreased or minimal response to the second vaccine. Thus, further investigation is warranted.

The limitations included the small number of patients and lack of a predefined sample collection. Although the anti-S antibody level is an important determinant for the protection against the infection, T-cell mediated cellular immunity also plays an important role against viral infection [12, 13]. The T-cell response to vaccination was not evaluated. The study was also limited because the clinically protective antibody levels were based on the original SARS-Cov-19 strain, and more recent delta or omicron variant strains were not considered. Therefore, it is necessary to re-evaluate the protective effect for these strains. Given the small number of patients included in our study and the retrospective nature of the analysis, it was not possible to definitively identify the predictor of the response to the vaccine. Thus, further investigation is required.

In conclusion, the second dose of vaccine resulted in antibody production in most HSCT patients. However, clinically protective levels of antibody were obtained in 77% of allo-HSCT and 46% of auto-HSCT recipients. The main factors influencing the protective level of antibody response were the number of CD19 + cells and serum IgG levels in allo-HSCT and auto-HSCT patients. This antibody response was also influenced by the post-transplant period, complete remission status, use of immunosuppressive drugs as well as the level of lymphocyte subsets, including CD4, CD8, and CD56 positive cells. The reconstitution of cellular and humoral immunity in HSCT patients might be closely related to their ability to produce antibodies following vaccination. Larger and and more detailed investigations are warranted to gain new insights on the immunological reconstitution in transplant patients and to guide further vaccination programs.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12185-022-03325-9.

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Author contributions TaT conceived and designed the study, collected data, performed the statistical analysis, wrote the manuscript, and provided patient care. TY, YK, DI, AK, RT, TeT, DM, KN, and MT provided patient care. KM initiated, designed, and supervised the study, collected data, wrote the manuscript, and provided patient care. All authors reviewed and approved the manuscript.

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Availability of data and material The datasets generated during and/or analyzed during the current study are available from Takafumi Tsushima or Kosei Matsue on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by each institutional review board (Approval Number:21–025).

Consent to participate All participants or their family members provided written informed consent for study participation.

Consent for publication Patients signed informed consent regarding publishing their data and photographs.

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