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Serological response 5 months after the BNT162b2 COVID-19 vaccination in patients with various hematological disorders in Japan

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Purpose: Patients with hematological malignancies are at an increased risk of severe infection with coronavirus disease 2019 (COVID-19). However, developing an adequate immune response after vaccination is difficult, especially in patients with lymphoid neoplasms. Since the long-term effects of the BNT162b2 vaccine are unclear, the humoral immune response 5 months after the two vaccinations in patients with hematological disorders was analyzed.

Materials and Methods: Samples were collected from 96 patients vaccinated twice with BNT162b2 and treated with at least one line of an antitumor or immunosuppressive drug in our hospital from November 2021 to February 2022. Serum anti-severe acute respiratory syndrome coronavirus 2 (anti-SARS-CoV-2) spike (S) antibody titers were analyzed. Patients were age- and sex-matched using propensity matching and compared with a healthy control group. Patients with serum anti-SARS-CoV-2 S antibodies were defined as 'responder' if >50 U/mL. The patients had B-cell non-Hodgkin lymphoma (B-NHL), multiple myeloma, chronic myeloid leukemia, etc.

Results: Patients had significantly low antibody levels (median, 55.3 U/mL vs. 809.8 U/mL; $p<0.001$) and a significantly low response rate ($p<0.001$). Multivariate analysis showed that patients with B-NHL, aged >72 years, were associated with a low response to vaccination. There were no significant differences between patients with chronic myeloid leukemia and healthy controls.

Conclusion: Our study shows that patients with hematological disorders are at risk of developing severe COVID-19 infections because of low responsiveness to vaccination. Moreover, the rate of antibody positivity differed between the disease groups. Further studies are warranted to determine an appropriate preventive method for these patients, especially those with B-NHL.

Keywords: BNT162 vaccine, COVID-19, Hematologic diseases, B-cell lymphoma, Chronic myeloid leukemia

Introduction

The World Health Organization declared a coronavirus disease 2019 (COVID-19) pandemic in March 2020, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Several factors contribute to the severity of COVID-19, and patients with hematological malignancies are at high risk of life-threatening SARS-CoV-2 infection. Immunodeficiency due to disease or immunosuppressive treatment results in mortality rates exceeding 30% [2,3]. The BNT162b2 vaccine was developed to counter

the COVID-19 pandemic, and its efficacy was confirmed in a placebo-controlled phase 3 trial [4]. To prevent infection and reduce serious respiratory failure, effective vaccines against SARS-CoV-2 have been developed and rapidly approved by the Ministry of Health, Labour, and Welfare of Japan, including the BNT162b2 COVID-19 vaccine, which has been available in Japan since February 2021 [5]. The immunogenicity of this messenger RNA (mRNA) vaccine is induced by antibody-mediated humoral and SARS-CoV-2 spike (S) protein-specific $CD8^+$ T lymphocytes responses [6]. Although vaccines for immunocompetent individuals have shown clear benefits in protecting against severe COVID-19, the advantages of vaccinations for immunologically vulnerable patients with hematological malignancies remain insufficient. A previous report showed that patients with hematological malignancies did not develop potent immunological responses after vaccination [7]. In addition, the absence of serum antibody responses is associated with prolonged viral shedding of SARS-CoV-2 [8]. In another report, patients with lymphoid neoplasms, especially B-cell lymphoma after anti-CD20 monoclonal antibodies therapy, showed low responsiveness 2 weeks after the BNT162b2 vaccine [9]. Such reports have analyzed the vaccine effect within 2 weeks to 2 months [7,9-11], but the long-term effects of BNT162b2 remain unclear.

A comparison of humoral immune responses between patients with various hematological diseases and healthy controls is required to identify patients at risk of severe COVID-19. The present study aimed to investigate the serological response 5 months after the BNT162b2 vaccination in patients with various hematological disorders.

Materials and Methods

This single-center observational study assessed the serological response after administering the BNT162b2 vaccine twice in patients with hematological disorders. Patients diagnosed and treated at Nagoya Memorial Hospital, Japan, between November 2021 and February 2022 were included in this study. All patients received two doses of the BNT162b2 vaccine and underwent at least one line of chemotherapy or were treated with immunosuppressive drugs. Data were collected from electronic medical records, including hematological diagnoses and treatments, date of treatment, and whether the patients were infected with SARS-CoV-2 from the time of blood sampling until the end of February 2022. All participants completed a questionnaire related to their history of COVID-19 and date of vaccine administration. Participants with a known history of COVID-19 before blood collection or other COVID-19 vaccines were excluded. Blood samples were collected after the second and third vaccination sessions. The patients were compared with healthy donors who belonged to our institute and were >20 years old. Age- and sex-matched groups were created using propensity score matching. This study was approved by the local institutional review board, and all participants signed an informed consent form.

Serological tests for antibody titers against SARS-CoV-2 were performed using the Elecsys anti-SARS-CoV-2 S assay on a Cobas e601 (Roche Diagnostics, Rotkreuz, Switzerland) enzyme-linked immunosorbent assay reader, for the quantitative detection of antibodies, predominantly immunoglobulin G (IgG), targeting the SARS-CoV-2 S protein receptor-binding domain [12]. This assay had a measurement range of 0.40–250 U/mL, with a concentration of <0.80 U/mL considered a negative result and of ≥0.80 U/mL considered a positive result. When the results exceeded the upper limit of the measurement range, the samples were diluted from 1:10 to 1:100, depending on the required dilution range. Based on a previous report of a positive association between antibody titer and neutralizing antibody activity [10], patients with an antibody titer ≥50 U/mL were defined as "responders," and those with an antibody titer <50 U/mL were defined as "non-responders," to investigate antibody-mediated inhibition of infection.

For statistical analysis, the Mann-Whitney U test was used to compare continuous variables, and Fisher's exact test was used to analyze categorical variables. To compare the differences in antibody titers between healthy controls and each disease group, comparisons were performed using the Kruskal-Wallis test when the groups contained nine or more patients. To estimate the propensity score, a logistic regression model was fitted for the serological response rate, with age and sex as patient stratification factors. The baseline variables ($p<0.10$) in the univariate analysis were included in the multivariate models. The threshold for significance was set at $p<0.05$. All statistical analyses were conducted using EZR in R commander ver. 1.55 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/) [13].

Results

Participants

One hundred patients were recruited between November

2021 and February 2022. One patient did not receive any therapy, and blood samples could not be collected from another patient because of disease progression. Two patients were excluded: one was vaccinated with mRNA-1273, and the other had a known history of COVID-19 before blood samples were obtained. As a result, 96 patients with various hematological diseases and 352 healthy controls were included in the analysis. The baseline characteristics of the patients and healthy controls are presented in Table 1. The median age of the patients was 72 years (interquartile range [IQR], 62–79 years), and 47 patients (49%) were male. Compared to the healthy controls, the patients were significantly older (median age of the control group, 39 years; IQR, 28–49 years; p<0.001) and predominantly male (n=62 [18%], p<0.001). Their diseases were as follows: B-cell non-Hodgkin lymphoma (B-NHL; n=29), multiple myeloma (MM; n=21), chronic myeloid leukemia (CML; n=9), immune thrombocytopenia (ITP; n=9), acute myeloid leukemia (AML; n=6), myelodysplastic syndrome (MDS; n=5), and others (n=17, including four patients with aplastic anemia, three patients each with paroxysmal nocturnal hematuria and essential thrombocytosis, two patients with pure red cell aplasia, and one each with angioimmunoblastic T cell lymphoma, classic Hodgkin lymphoma, acute lymphoblastic leukemia, polycythemia vera, and hypereosinophilic syndrome). These patients had a median of one treatment line (range, 1–5 lines) and a median number of days from treatment initiation to obtaining a sample was 706.5 days (IQR, 393.5–1,843.2 days). Seventy-five patients (78%) were under treatment, and the remaining 21 patients had a median of 357 days (IQR, 173.0–509.0 days) since the end of treatment at the date of obtaining the blood sample.

Comparisons between patients with hematological disorders and healthy controls

When analyzed as a whole, the rates of the responders were significantly low (51% versus 99%; odds ratio [OR], 0.006; 95% CI, <0.00–0.023; p<0.001), and the patients had significantly lower antibody titers (median [IQR], 55.3 [6.9–224.4] U/mL versus 809.8 [506.1–1,292.3] U/mL; p<0.001) (Fig. 1A) compared to the control group, while the time from second vaccination to serological assay was similar (median [IQR], 160.0 [119.0–180.2] days versus 160.5 [159.0–162.0] days; p=0.543).

Propensity score matching was performed to match the age and sex with the patient group. Based on age- and sex-matched controls, patients with hematological disorders were significantly less likely to be responders (63% versus 100%, respectively; OR, 0.066; 95% CI, 0.001–0.51; p<0.001) and had lower antibody titers (median [IQR], 115.9 [12.6–475.2] U/mL versus 781.9 [413.6–1,179.0] U/mL; p<0.001] (Fig. 1B). In addition, when propensity score analysis was applied, the time from the second vaccination to serological as-

Table 1. Baseline characteristics of patients and healthy controls

Characteristic	All the subjects			Matched subjects		
	Patients with hematological disorder	Healthy control	p-value	Patients with hematological disorder	Healthy control	p-value
No. of patients	96	352		32	32	
Age (yr)	72.0 (62.0–79.0)	39.0 (28.0–49.0)	<0.001	51.5 (43.8–62.0)	54.5 (43.8–62.0)	0.88
Male sex	47 (49.0)	62 (18.0)	<0.001	12 (38.0)	9 (28.0)	0.56
Time from 2nd vaccination (day)	160.0 (119.0–180.2)	160.5 (159.0–162.0)	0.54	128.5 (98.3–156.3)	160.0 (159.0–161.0)	<0.001
Disease group						
B-NHL	29 (30.0)	NA	NA	7 (22.0)	NA	0.45
MM	21 (22.0)	NA	NA	4 (13.0)	NA	0.31
AML/MDS	11 (12.0)	NA	NA	2 (6.2)	NA	0.52
CML	9 (9.4)	NA	NA	5 (16.0)	NA	0.34
ITP	9 (9.4)	NA	NA	6 (19.0)	NA	0.20
Others	17 (18.0)	NA	NA	8 (25.0)	NA	0.44
Antibody titer (U/mL)	55.3 (6.9–224.4)	809.8 (506.1–1,292.3)	<0.001	115.9 (12.6–475.2)	781.9 (413.6–1,179.0)	<0.001
Responder	49 (51.0)	350 (99.0)	<0.001	20 (63.0)	32 (100.0)	<0.001

Values are presented as number, median (interquartile range), or number (%).
NA, not applicable; B-NHL, B cell non-Hodgkin lymphoma; MM, multiple myeloma; AML/MDS, acute myeloid leukemia/myelodysplastic syndrome; CML, chronic myeloid leukemia; ITP, immune thrombocytopenia.

say was significantly shorter in the patients than that in the controls (median [IQR], 128.5 [98.3–156.3] days versus 160.0 [159.0–161.0] days; p<0.001) (Table 1).

Compared to controls, patients with B-NHL (n=29), MM (n=21), AML/MDS (n=11), and ITP (n=9) had significantly lower antibody titers after two rounds of BNT162b2 vaccination, whereas those with CML (n=9) did not have lower titers (p=0.31) (Fig. 2). The patients with AML were elderly people (median, 78.5 years; IQR, 71.5–83.0 years), and the majority were not candidates for intensive chemotherapy; thus, pa-

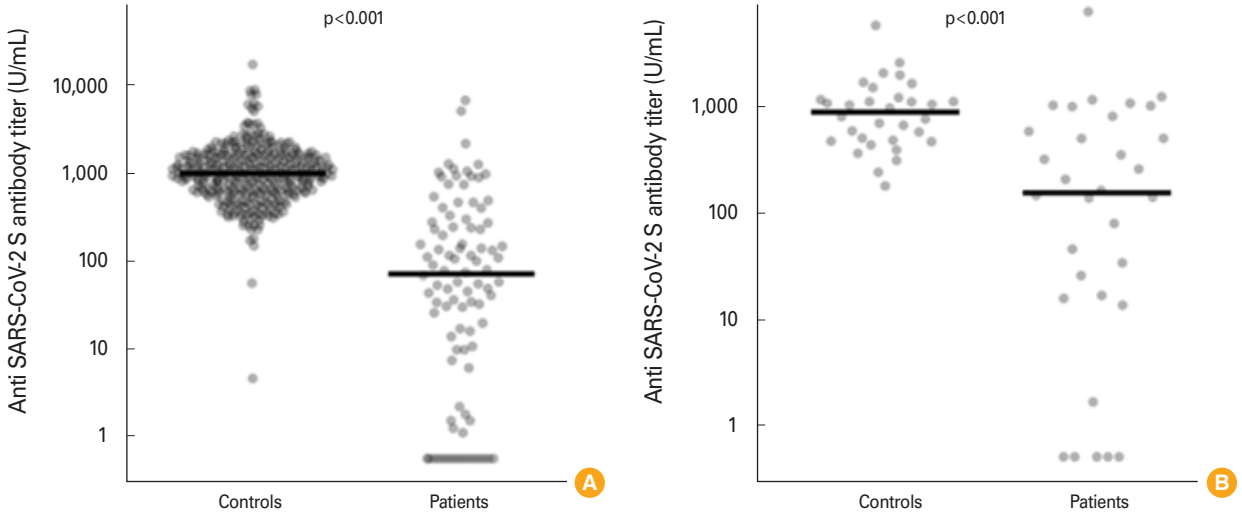

Fig. 1. Anti-severe acute respiratory syndrome coronavirus 2 (anti-SARS-CoV-2) spike (S) antibody titers among patients with hematological disorders. Anti SARS-CoV-2 S antibody titer obtained from patients with hematological disorders was compared with those obtained from healthy controls in all subjects or matched populations. The Mann-Whitney U test was used for comparison. **(A)** All subjects with hematological disorders and healthy controls. **(B)** Patients with significantly lower anti-SARS-CoV-2 antibody titers compared with age- and sex-matched healthy controls using propensity score matching methods.

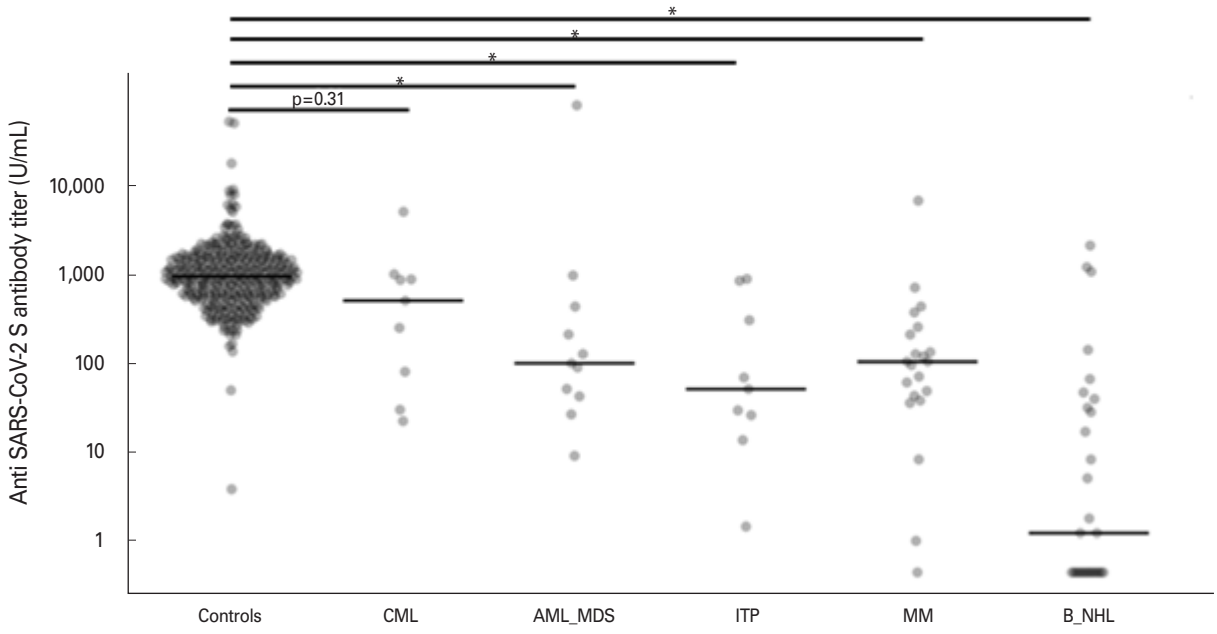

Fig. 2. Comparison of anti-severe acute respiratory syndrome coronavirus 2 (anti-SARS-CoV-2) spike (S) antibody titers between controls and patients in each group. Differences in anti-SARS-CoV-2 S antibody titers were compared between healthy controls and individual hematological disorder groups, including chronic myeloid leukemia (CML), acute myeloid leukemia/myelodysplastic syndrome (AML_MDS), immune thrombocytopenia (ITP), multiple myeloma (MM), and B-cell non-Hodgkin lymphoma (B_NHL). Group comparisons were performed using the Kruskal-Wallis test when the groups contained nine or more patients. *p<0.001.

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tients with AML/MDS were grouped together to compare the effect of the azacitidine (hypomethylating agent) treatment on the response invoked by BNT162b2.

SARS-CoV2 antibody titers in patients with hematological disorders

Detailed baseline characteristics of the patients with hematological disorders and the antibody titers in each group are shown in Table 2. All 29 patients with B-NHL received anti-CD20 antibodies (n=27) or Bruton's tyrosine kinase (BTK) inhibitors (n=3). The serological response rates with vaccination and median antibody titers of anti-CD20 antibody therapy were 19% and 1.1 U/mL (IQR, 0.4–32.9 U/mL), respectively. Among the 15 patients (52%) undergoing chemotherapy, 13 (87%) failed

Table 2. Characteristics and antibody titer of patients and responders

Variable	All patients (n=96)	No. of responder (%) (n=49)	Median antibody titer (IQR) (U/mL)
Diagnosis			
B cell non-Hodgkin lymphoma	29	5 (17)	1.1 (0.4–27.6)
Multiple myeloma	21	14 (67)	90.1 (37.5–181.4)
Chronic myeloid leukemia	9	7 (78)	433.9 (69.7–750.1)
Immune thrombocytopenia	9	4 (44)	44.6 (22.8–262.3)
Acute myeloid leukemia	6	3 (50)	77.1 (38.9–306.5)
Myelodysplastic syndrome	5	4 (80)	86.6 (77.9–181.9)
Aplastic anemia	4	3 (75)	157.3 (91.3–294.6)
Paroxysmal nocturnal hematuria	3	3 (100)	323.3 (256.4–558.1)
Essential thrombocytosis	3	2 (67)	154.9 (80.2–273.3)
Others (no. of patients ≤2)	7	4 (57)	85 (11.6–171.8)
Treatment			
B cell non-Hodgkin lymphoma			
Anti-CD20 antibodies	27	5 (19)	1.1 (0.4–32.9)
BTK inhibitor	3	0	0.4 (0.4–0.4)
Multiple myeloma			
Anti-CD38 antibody	10	5 (50)	66.5 (34.3–112.4)
Proteasome inhibitors	21	14 (67)	90.1 (37.5–181.4)
Immunomodulatory drugs	15	11 (73)	90.1 (47.7–148.4)
Myeloid malignancies			
BCL-2 inhibitor	4	1 (25)	40.9 (33.6–240.4)
Hypomethylating agent	7	5 (71)	86.6 (57.5–504.7)
Bcr-Abl TKIs	9	7 (78)	433.9 (69.7–750.1)
Immunosuppressants			
Prednisolone	12	6 (50)	52.3 (20.1–243.9)
Cyclosporin	5	2 (40)	10.4 (0.8–121.6)
C5b monoclonal antibody	3	3 (100)	323.3 (256.4–558.1)
Lines of treatment			
1 Line	55	27 (49)	37.5 (3.6–250.1)
2 Lines	26	16 (62)	60.8 (27.7–187.5)
Over 3 lines	15	6 (40)	42.4 (4.3–167.6)
Time from last treatment (day)			
On therapy	75	41 (55)	69.7 (9.2–228.85)
<365	11	3 (27)	1.1 (0.4–40.5)
≥365	10	5 (50)	111.2 (29.4–777.8)
Time from treatment initiation (day)			
2nd vaccine before treatment	16	9 (56)	67.8 (13–121.8)
<706	32	10 (31)	24.7 (0.4–87.6)
≥706	48	30 (63)	44.7 (25.1–377.6)

IQR, interquartile range.

to respond to vaccination. Compared with the responders, they tended to be older (median age [IQR], 75 [54–88] years versus 60 [49–71] years; p=0.061). Fourteen patients (48%) completed treatment, and 3 (21%) responded to vaccination.

Of the 21 patients with MM, anti-CD38 antibodies, proteasome inhibitors, and immunomodulatory drugs were administered to 10, 21, and 15, respectively. The proportions of responders for each drug treatment were 50%, 67%, and 77%, respectively, and the median titers of the antibody were 66.5 U/mL (IQR, 34.3–112.4 U/mL), 90.1 U/mL (IQR, 37.5–181.4 U/mL), and 90.1 U/mL (IQR, 47.7–148.4 U/mL), respectively. Of the 17 patients under treatment, 7 (41%) failed to respond to vaccination.

Among patients with myeloid malignancies, 4 (20%) received BCL2 inhibitors, 7 (35%) received hypomethylating agents, and 9 (45%) with CML received tyrosine kinase inhibitors (TKIs). The proportion of responders per treatment was 25%, 71%, and 78%, respectively, and the median antibody titers were 40.9 U/mL (IQR, 33.6–24.4 U/mL), 86.6 U/mL (IQR, 57.5–504.7 U/mL), and 433.9 U/mL (IQR, 69.7–750.1 U/mL), respectively.

The rates of responders among patients treated with immunosuppressants (n=19), such as prednisolone (n=12), cyclosporin (n=5), or C5b monoclonal antibody administered for paroxysmal nocturnal hematuria (n=3), were 50%, 40%, and 100%, respectively, and the median titers of the antibody were 52.3 U/mL (IQR, 20.1–243.9 U/mL), 10.4 U/mL (IQR, 0.8–121.6 U/mL), and 323.3 U/mL (IQR, 256.4–558.1 U/mL), respectively.

Univariate analysis of the response to the BNT162b2 vaccine in hematological patients is shown in Table 3. In the univariate analysis, age >72 years, diagnosis of B-NHL, and time from hematological treatment initiation of <706 days were significantly associated with a lower response rate to the vaccine. Sex, line of treatment, and time since the last treatment did not significantly affect the response rate. In the multivari-

Table 3. Univariate analysis of serological response in patients with hematological disorders

Variable	Responder	Non-responder	Total	p-value	OR (95% CI)
No. of patients	49	47	96		
Age (yr)				0.024	0.36 (0.15–0.89)
≤72	31 (63)	18 (37)	49		
>72	18 (38)	29 (62)	47		
Sex				0.69	1.18 (0.49–2.85)
Male	25 (53)	22 (47)	47		
Female	24 (49)	25 (51)	49		
Disease group				<0.001	
B-NHL	5 (17)	24 (83)	29	<0.001	0.11 (0.029–0.35)
MM	14 (67)	7 (33)	21	0.14	2.27 (0.75–7.43)
AML/MDS	7 (64)	4 (36)	11	0.52	1.78 (0.42–8.93)
CML	7 (78)	2 (22)	9	0.16	3.70 (0.66–38.5)
ITP	4 (44)	5 (56)	9	0.74	0.75 (0.14–3.74)
Others	12 (71)	5 (29)	17	0.11	2.70 (0.79–10.7)
Lines of treatment				0.69	1.20 (0.49–2.92)
1 Line	27 (49)	28 (51)	55		
≥2 Lines	22 (60)	19 (40)	41		
Time from last treatment (day)				0.24	
On therapy	41 (55)	34 (45)	75	0.22	1.95 (0.66–6.10)
≤357	3 (27)	8 (73)	11	0.12	0.32 (0.051–1.46)
>357	5 (50)	5 (50)	10	1.00	0.95 (0.20–4.48)
Time from treatment initiation (day)				0.021	
2nd vaccination before treatment	9 (56)	7 (44)	16	0.79	1.28 (0.38–4.48)
<706	10 (31)	22 (69)	32	0.009	0.30 (0.11–0.78)
≥706	30 (63)	18 (38)	48	0.04	2.52 (1.04–6.29)

Values are presented as number, number (%), or OR (95% CI).
OR, odds ratio; CI, confidential interval; B-NHL, B cell non-Hodgkin lymphoma; MM, multiple myeloma; AML/MDS, acute myeloid leukemia/myelodysplastic syndrome; CML, chronic myeloid leukemia; ITP, immune thrombocytopenia.

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Table 4. Multivariate analysis of serological response in patients with hematological disorders

Variable	OR (95% CI)	p-value
Age >72 yr	0.056 (0.011–0.30)	<0.001
Disease group with B-NHL	0.070 (0.016–0.30)	<0.001
Time from treatment initiation <706 days	0.46 (0.15–1.40)	0.17

OR, odds ratio; CI, confidential interval; B-NHL, B-cell non-Hodgkin lymphoma.

ate analysis of serological response, age >72 years and a diagnosis of B-NHL were significantly associated with a lower response rate to the vaccine (Table 4).

Outcome

We investigated the number of COVID-19 infections during the study period. By the end of the observation period, three patients had breakthrough vaccine infection with SARS-CoV-2. One of the three patients who responded to the BNT162b2 vaccine had CML and mild COVID-19. The other two patients had ITP and B-NHL and were non-responders. In a patient with ITP, COVID-19 showed improvement with sotrovimab, a monoclonal neutralizing antibody drug. The patient with B-NHL only had moderate COVID-19 after treatment with anti-CD20 antibody. However, the patient subsequently required long-term immunosuppressive treatment for interstitial pneumonia caused by COVID-19.

Discussion

Decreased titers of antibodies targeting the SARS-CoV-2 S protein receptor-binding domain have been observed in patients with various hematological disorders. The antibody titers and rates of responders were significantly lower in patients 5 months after receiving two doses of the BNT162b2 vaccine in patients with hematological disorders than in healthy controls. Since some factors have been reported to influence the antibody positivity rate, including age and female sex [14], patients were compared with age- and sex-matched controls using propensity score analysis. Patients with hematological disorders had significantly lower antibody titers and response rates than age- and sex-matched controls, although the time from the second vaccine to the serological assay was significantly shorter in this group. A previous report has shown that a longer time from the second vaccine administration to the date of blood collection was associated with lower titers of SARS-CoV-2 S antibodies [15].

Patients showed various antibody responses depending on the disease group. In the present cohort, patients with B-NHL treated with an anti-CD20 antibody or a BTK inhibitor and those with AML treated with a BCL2 inhibitor tended to have a low antibody response rate. These treatments suppress B cell differentiation and proliferation, essential for immune response. Thus, the response to the mRNA vaccination is insufficient, as shown by Okamoto et al. [9]. Several reports have shown that patients treated with anti-CD20 antibodies, BCL2 inhibitors, BTK inhibitors, or JAK inhibitors are at risk of low serological response [7,16]. In fact, patients with COVID-19 compromised by these agents show severe inflammation because of early viral shedding failure [17].

Seven of the nine patients with CML showed a similar response to the BNT162b2 vaccine as the control group, and the remaining two patients did not respond to the vaccine (antibody titers of 19.6 U/mL and 26.2 U/mL, respectively). The median age of the former seven patients was 59 years (range, 42–81 years), and the ages of the latter two patients were 87 years and 90 years. This suggests that TKIs have a limited effect on humoral response induced by the BNT162b2 vaccine and that the patient's age is important, although the off-target effects of TKIs on c-kit and PDGFR may affect lymphocyte function. This finding supports the fact that the probability of antibody acquisition was significantly lower in the group aged >72 years based on multivariate analysis (Table 4). In another report, Katagiri et al. [18] showed the effectiveness of two BNT162b2 vaccines in patients with CML treated with TKIs compared to healthy controls.

To optimize the timing of the BNT162b2 vaccine administration, the effects of the time from the last treatment and the time from treatment initiation on the antibody response rate were evaluated. The response to the BNT162b2 vaccine was significantly low in patients at 0 to 706 days after the initiation of chemotherapy or immunosuppressants than at 706 days after the initiation of treatment in the univariate analysis, but this was not significant in the multivariate analysis. This result could be related to multiple confounding factors such as age, disease specificity, and duration of treatment. Regarding the time since the last treatment, some reports have shown a low response rate to the vaccine in patients receiving anti-CD20 antibodies within 12 months [19]. This is likely related to B cell reconstitution, which takes approximately 9–12 months after treatment with rituximab, an anti-CD20 antibody [20].

The present study has several limitations. One challenge is that immunocompetence is difficult to assess based only on antibody levels. Other immune functions, such as those of T

cells, have not been evaluated, although antibody titers are useful surrogates for evaluating humoral immunity. Moreover, the timing of sample collection was not uniform, owing to restrictions caused by the COVID-19 pandemic. In addition, S antibody activity was measured rather than neutralizing antibody activity, indicating that it was impossible to show a direct relationship between the SARS-CoV-2 S antibody titer and the inhibition of COVID-19 infection. A previous report showed a correlation between the Elecsys anti-SARS-CoV-2 S and neutralizing antibody assays [10]. Finally, an increase in antibody titers due to asymptomatic SARS-CoV-2 infection could not be excluded during the assessment.

Although some patients showed poorer responses to the vaccine than healthy individuals, many patients benefited from the vaccine. The findings of this study suggest that a third booster vaccination with SARS-CoV-2 mRNA is important for responders after the second vaccination. However, a recent report showed that a third booster BNT162b2 vaccination was only effective in one-third of patients with hematological malignancies who failed to achieve seroconversion after the second vaccination [21].

Vaccine reactivity in hematologic diseases varies but shows modest efficacy. Appropriate vaccination strategies for each disease and treatment may help establish protection against COVID-19. Further vaccine research with a multifaceted approach is warranted to develop an optimal method to prevent patients with hematological disorders from suffering from severe COVID-19.

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