

A Prospective Study Regarding the Efficacy and Safety of the BNT162b2 Vaccine in Patients With Solid Malignancies Undergoing Systemic Chemotherapy

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Abstract. *Background/Aim:* To prospectively evaluate the efficacy and safety of the BNT162b2 vaccine in solid cancer patients undergoing systemic chemotherapy (n=63). *Patients and Methods:* COVID-19 anti-spike protein antibody levels were measured before the first BNT162b2 vaccination, just before the second BNT162b2 vaccination, one month after the second BNT162b2 vaccination, and 3 months after the second BNT162b2 vaccination. Anti-spike protein antibody seropositivity was set at ≥ 0.8 U/ml. *Results:* Colorectal cancer was the most commonly observed primary disease (36.5%). ECOG-PS 0 was observed in the majority (52.4%) of patients. The overall response rate and the median (range) anti-spike protein antibody levels in the whole cohort at 3 months after the second BNT162b2 vaccination were 98.4% (62/63) and 206 (0.4-3,813) U/ml. None of the patients

required postponement or discontinuation of systemic chemotherapy because of an adverse reaction. *Conclusion:* The BNT162b vaccine in solid cancer patients undergoing systemic chemotherapy is effective and safe.

The COVID-19 pandemic is still ongoing, and antibody acquisition against COVID-19 through vaccination is necessary for infection control (1, 2). Currently, several COVID-19 vaccines are under development worldwide (3, 4). Three types of COVID-19 vaccines [Pfizer (BNT162b2), Moderna (mRNA-1273), and AstraZeneca (ChAdOx1 nCov19)] are currently approved in Japan, all of which have shown high efficacy (94-95%) in preventing the onset of symptomatic COVID-19 (5-7).

The Pfizer BNT162b2 vaccine is a lipid nanoparticle-formulated, nucleoside-modified RNA (mRNA) vaccine encoding a prefusion-stabilized, membrane-anchored severe acute respiratory syndrome coronavirus 2 full-length spike protein (8). In Japan, the BNT162b2 mRNA vaccine was approved by the regulatory authorities in February 2021, with priority vaccination for healthcare workers. Priority vaccination for the elderly and patients with underlying diseases had also been initiated in April 2021. Reports have begun to emerge from both Japan and overseas on the rate of antibody acquisition and reduction of COVID-19 infection rates through vaccination for COVID-19 in healthy subjects (8-11). On the other hand, cancer patients have a significantly higher incidence, severity, and mortality rate of COVID-19 infection, and patients with solid tumors are also priority

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Key Words: BNT162b2 vaccine, advanced cancer, systemic chemotherapy, efficacy, safety.



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Our prospective study regarding the efficacy and safety of the BNT162b2 vaccine in patients with solid malignancy undergoing systemic chemotherapy

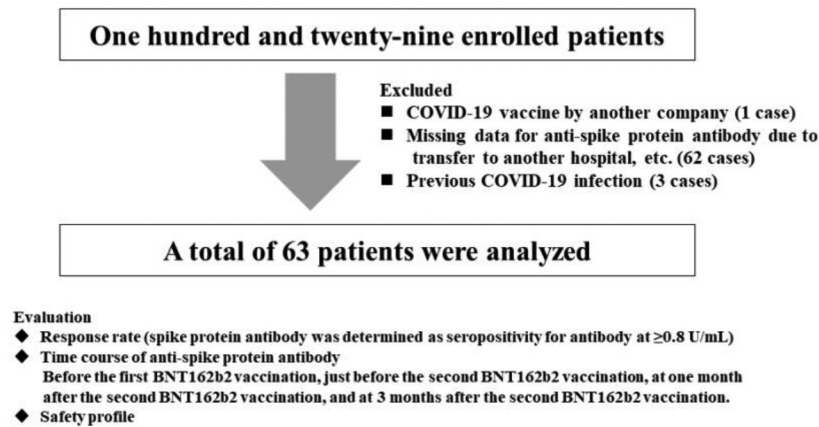


Figure 1. Study design.

candidates for vaccination. Early vaccination of cancer patients is also recommended in the NCCN guidelines (12), but evidence supporting the safety and efficacy of vaccines for cancer patients, especially those undergoing systemic chemotherapy, is scarce (13, 14). In an overseas phase III study that examined the effectiveness of BNT162b2, 80% of the participants were healthy individuals with no underlying disease, and the percentage of participants with malignant disease in the BNT162b2 vaccine group was as low as 3.9%, but these details are not available (9). An observational study of approximately 29,000 cancer patients who received the BNT162b2 vaccine has been published (15). This study showed that two doses of the BNT162b2 vaccine reduced the risk of infection, even in cancer patients, and the vaccine was 58% effective in reducing the risk of infection. The risk reduction effect of the BNT162b2 vaccine in non-cancer patients was more than 90%, suggesting that the vaccine may be less effective in cancer patients (15). However, data for cancer patients with systemic chemotherapy are not available in that study (15). Therefore, it would be highly significant to conduct an observational study to investigate the efficacy and safety of BNT162b2.

Based on this background, in this prospective study, we sought to evaluate the efficacy and safety of the BNT162b2 vaccine in solid cancer patients undergoing systemic chemotherapy.

Patients and Methods

Study design. The study subjects were solid tumor patients undergoing systemic chemotherapy at the Outpatient Chemotherapy Center and the Breast Surgery Outpatient Clinic in the Osaka

Medical and Pharmaceutical University Hospital between May 2021 and November 2021, who agreed to participate in our prospective study. Cases meeting any of the following conditions were excluded: 1) patients aged less than 20 years, 2) patients not expected to survive longer than 6 months, 3) patients receiving intensive corticosteroid therapy or immunosuppressive therapy except for cases of prophylactic corticosteroid therapy for chemotherapy-induced nausea and vomiting, 4) patients with hematological disease, and 5) patients receiving intensive systemic chemotherapy with the long-term persistent myelosuppressive condition.

COVID-19 anti-spike protein antibody levels were measured before the first BNT162b2 vaccination, just before the second BNT162b2 vaccination (patients received two BNT162b2 vaccine doses, 21 days apart) (Time A), at one month after the second BNT162b2 vaccination (Time B), and at 3 months after the second BNT162b2 vaccination (Time C). Anti-spike protein antibody was measured using Elecsys® Anti-SARS-Cov-2 S RUO (Roche diagnostics K.K., Tokyo, Japan). Anti-spike protein antibody seropositivity was determined at ≥ 0.8 U/ml (16). A total of 129 patients were enrolled. One case with COVID-19 vaccine by another company, 62 cases in which anti-spike protein antibody measurements could not be performed before and after BNT162b2 vaccination due to transfer to another hospital, and 3 cases confirmed as previously infected with COVID-19 were excluded from the analysis, leaving 63 cases for the final analysis (Figure 1).

Response rates for the BNT162b2 vaccine (percentage of seropositivity for anti-spike protein antibody), the time course of anti-spike protein antibody levels, and safety profiles were evaluated for all cases and compared according to sex, age, ECOG-PS, body mass index (BMI), serum albumin level, total lymphocyte count, corticosteroid use and immune checkpoint inhibitor (ICI) therapy. The safety profile was evaluated using the questionnaire of adverse reactions for all patients at the first and second BNT162b2 vaccination. The Ethics Committee of our hospital provided ethical approval (approval number, 2021-010). Written informed consent was obtained from all included patients.

Table I. Baseline characteristics (n=63).

	n (%) or median (range)
Age (years)	70 (35-87)
Sex, male/female	29 (46.0)/34 (54.0)
ECOG-PS, 0/1/2	33 (52.4)/25 (39.7)/5 (7.9)
Body mass index (kg/m ²)	22.0 (16.1-31.8)
Disease clinical stage, I/II/III/IV	1 (1.6)/2 (3.2)/8 (12.7)/52 (82.5)
Primary disease	
Esophageal cancer	3 (4.8)
Gastric cancer	15 (23.8)
Colorectal cancer	23 (36.5)
Pancreatic cancer	5 (7.9)
Breast cancer	7 (11.1)
Others	10 (15.9)
Underlying disease	
Hypertension	22 (34.9)
Chronic hepatitis B	13 (20.6)
Hyperlipidemia	12 (19.0)
Diabetes	12 (19.0)
Hyperuricemia	7 (11.1)
Cerebrovascular disease	4 (6.3)
Atrial fibrillation	3 (4.8)
Asthma	2 (3.2)
Chronic heart failure	1 (1.6)
Corticosteroid therapy, yes/no	36 (57.1)/27 (42.9)
ICI therapy, yes/no	7 (11.1)/56 (88.9)
Serum albumin (g/dl)	3.7 (2.3-3.7)
Total lymphocyte count (/μl)	1331 (359-7118)

ICI: Immune checkpoint inhibitor.

Statistics. In the analysis of continuous variables, the appropriate choice in paired *t*-test, unpaired *t*-test, and Mann-Whitney *U*-test was made to compare 2 groups. In the data presentation, median (range) was used. A *p*=0.05 was set at the significant level by the JMP ver. 16 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics. Baseline characteristics in this study [*n*=63, 29 males, median (range) age=70 (35-87) years] are shown in Table I. In terms of ECOG-PS, ECOG-PS 0 was seen in the majority (*n*=33, 52.4%) of patients. In terms of primary disease, colorectal cancer was the disease observed in the majority of cases (*n*=23, 36.5%), followed by gastric cancer (*n*=15, 23.8%). Regarding disease clinical-stage, stage IV was found in the majority of cases (*n*=52, 82.5%). All analyzed patients received standard chemotherapeutic regimens based on current guidelines. Corticosteroid therapy with the aim of symptom control was followed in 36 cases (57.1%). ICI therapy was performed in 7 cases (11.1%). Sixty-one patients received two doses of the BNT162b2 vaccine during systemic chemotherapy, and two received one dose of the BNT162b2 vaccine during systemic chemotherapy.

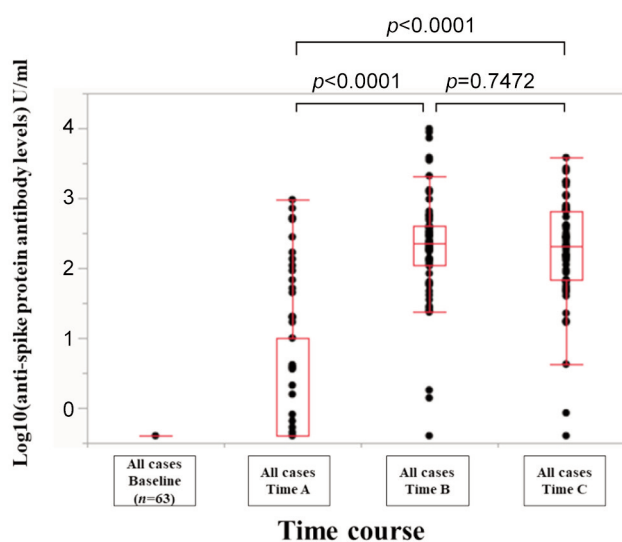


Figure 2. Log₁₀(anti-spike protein antibody levels) U/ml at baseline, Time point A (just before the second BNT162b2 vaccination), Time point B (1 month after the second BNT162b2 vaccination), and Time point C (3 months after the second BNT162b2 vaccination) for all cases.

Efficacy of BNT162b2 vaccine for all cases. The overall response rate in the whole cohort at the point of Time A (just before the second BNT162b2 vaccination), Time B (1 month after the second BNT162b2 vaccination) and Time C (3 months after the second BNT162b2 vaccination) was 34.9% (22/63), 96.8% (61/63) and 98.4% (62/63). The median (range) anti-spike protein antibody levels at the Time point A, B, and C were 0.4 (0.4-950) U/ml, 230 (0.4-9,871) U/ml, and 206 (0.4-3,813) U/ml (Time point A vs. Time point B, *p*<0.0001; Time point A vs. Time point C, *p*<0.0001; Time point B vs. Time point C, *p*=0.7472) (Figure 2).

Efficacy of BNT162b2 vaccine according to sex. In male (*n*=29) and female (*n*=34) patients, the response rate at the Time point A, B, and C was 24.1% (7/29), 100% (29/29) and 100% (29/29) in male patients, and 44.1% (15/34), 94.1% (32/34) and 97.1% (33/34) in female patients. The median (range) anti-spike protein antibody levels in male vs. female patients at the Time point A, B, and C was 0.4 (0.4-718) U/ml vs. 0.49 (0.4-950) U/ml at Time point A (*p*=0.1614), 182 (1.39-7,260) U/ml vs. 236.5 (0.4-9,871) U/ml at Time point B (*p*=0.5128), and 206 (16.8-2,436) U/ml vs. 196 (0.4-3,813) U/ml at Time point C (*p*=0.6505) (Figure 3).

Efficacy of BNT162b2 vaccine according to age. In younger (less than 65 years, *n*=19) and elderly (65 years or more, *n*=44) patients, the response rate at the Time point A, B, and C was 57.9% (11/19), 94.7% (18/19) and 100% (19/19) in younger patients, and 25.0% (11/44), 97.7% (43/44) and

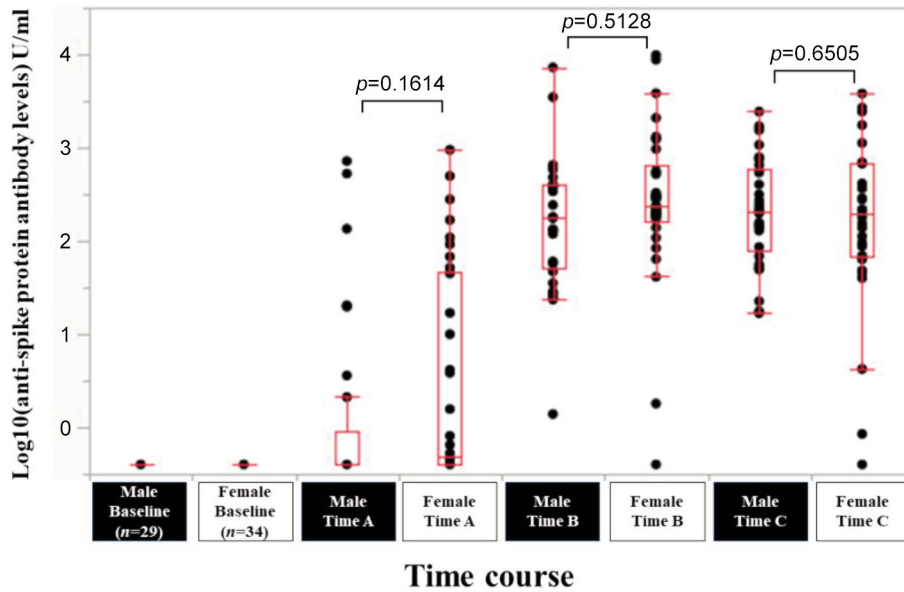


Figure 3. $\text{Log}_{10}(\text{anti-spike protein antibody levels}) \text{ U/ml}$ at baseline, Time point A, Time point B, and Time point C according to sex.

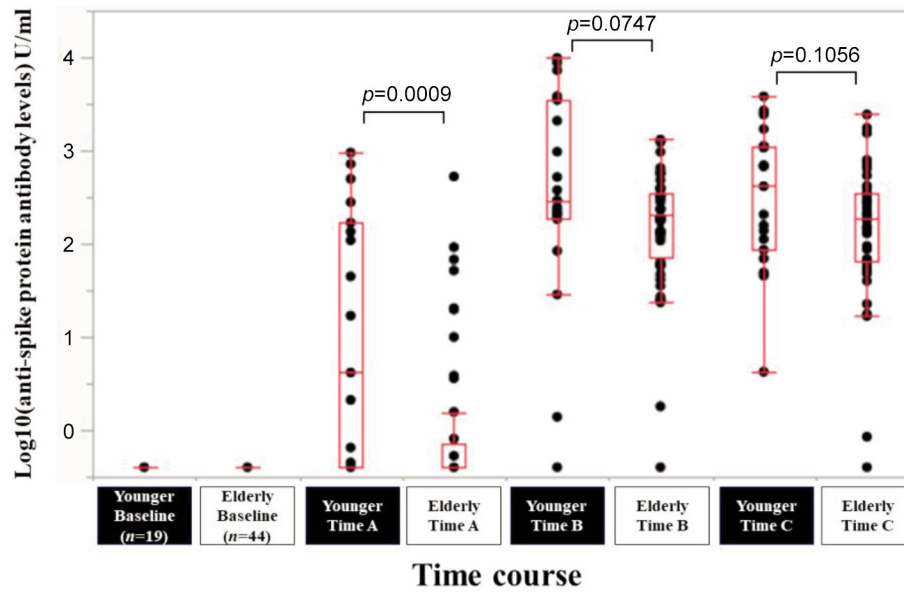


Figure 4. $\text{Log}_{10}(\text{anti-spike protein antibody levels}) \text{ U/ml}$ at baseline, Time point A, Time point B, and Time point C according to age (cutoff=65 years).

97.7% (43/44) in elderly patients. The median (range) anti-spike protein antibody levels in younger vs. elderly patients at the Time point A, B, and C were 4.2 (0.4-950) U/ml vs. 0.4 (0.4-527) U/ml at Time point A ($p=0.0009$), 294 (0.4-9,871) U/ml vs. 211 (0.4-1,310) U/ml at Time point B ($p=0.0747$), and 414 (4.23-3,813) U/ml vs. 191 (0.4-2,436) U/ml at Time point C ($p=0.1056$) (Figure 4).

Efficacy of BNT162b2 vaccine according to ECOG-PS. In patients with ECOG-PS 0 ($n=33$) and ECOG-PS 1 or 2 ($n=30$), the response rate at the Time point A, B, and C was 48.5% (16/33), 100% (33/33) and 100% (33/33) in patients with ECOG-PS 0, and 20.0% (6/30), 93.3% (28/30) and 96.7% (29/30) in patients with ECOG-PS 1 or 2. The median (range) anti-spike protein antibody levels in patients with

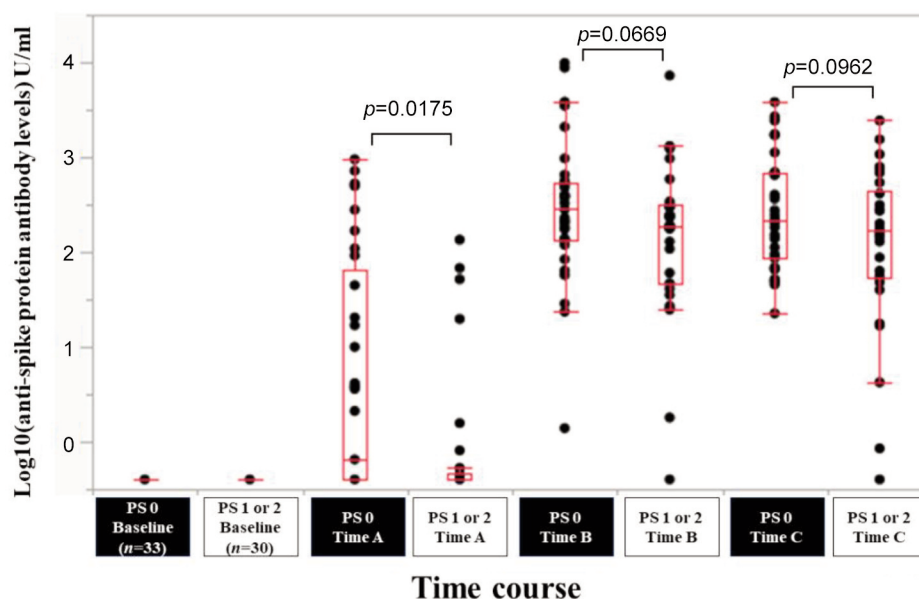


Figure 5. Log₁₀(anti-spike protein antibody levels) U/ml at baseline, Time point A, Time point B, and Time point C according to ECOG-PS.

ECOG-PS 0 vs. ECOG-PS 1 or 2 at the Time point A, B, and C were 0.4 (0.4-950) U/ml vs. 0.4 (0.4-135) U/ml at Time point A ($p=0.0175$), 287 (1.39-9,871) U/ml vs. 189.5 (0.4-7,260) U/ml at Time point B ($p=0.0669$), and 219 (22.6-3,813) U/ml vs. 168.5 (0.4-2,436) U/ml at Time point C ($p=0.0962$) (Figure 5).

Efficacy of BNT162b2 vaccine according to BMI. In patients with BMI >22 kg/m² ($n=31$) and BMI <22 kg/m² ($n=32$), the response rate at the Time point A, B, and C was 35.5% (11/31), 96.8% (30/31) and 96.8% (30/31) in patients with BMI >22 kg/m², and 34.4% (11/32), 96.9% (31/32) and 100% (32/32) in patients with BMI <22 kg/m². The median (range) anti-spike protein antibody levels in patients with BMI >22 kg/m² vs. BMI <22 kg/m² at the Time point A, B, and C were 0.4 (0.4-950) U/ml vs. 0.4 (0.4-718) U/ml at Time point A ($p=0.4,836$), 305 (0.4-9,871) U/ml vs. 189.5 (0.4-8,773) U/ml at Time point B ($p=0.1910$), and 276 (0.4-3,813) U/ml vs. 144.5 (0.85-2,682) U/ml at Time point C ($p=0.1604$) (Figure 6).

Efficacy of BNT162b2 vaccine according to serum albumin level. In patients with serum albumin <3.5 g/dl ($n=14$) and serum albumin ≥3.5 g/dl ($n=49$), the response rate at the Time point A, B, and C was 14.3% (2/14), 92.9% (13/14) and 100% (14/14) in patients with serum albumin <3.5 g/dl, and 40.8% (20/49), 98.0% (48/49) and 98.0% (48/49) in patients with serum albumin ≥3.5 g/dl. The median (range) anti-spike protein antibody levels in patients with serum albumin <3.5 g/dl vs. serum albumin ≥3.5 g/dl at the Time

point A, B, and C were 0.4 (0.4-950) U/ml vs. 0.4 (0.4-718) U/ml at Time point A ($p=0.1944$), 227 (0.4-970) U/ml vs. 230 (0.4-9,871) U/ml at Time point B ($p=0.3250$), and 179 (4.23-1,749) U/ml vs. 210 (0.4-3813) U/ml at Time point C ($p=0.7911$) (Figure 7).

Efficacy of BNT162b2 vaccine according to total lymphocyte count. In patients with total lymphocyte count <1,500/μl ($n=39$) and total lymphocyte count >1,500/μl ($n=24$), the response rate at the Time point A, B, and C was 25.6% (10/39), 97.4% (38/39) and 100% (39/39) in patients with total lymphocyte count <1,500/μl, and 50.0% (12/24), 95.8% (23/24) and 95.8% (23/24) in patients with total lymphocyte count >1,500/μl. The median (range) anti-spike protein antibody levels in patients with total lymphocyte count <1,500/μl vs. total lymphocyte count >1,500/μl at the Time point A, B, and C were 0.4 (0.4-950) U/ml vs. 1.255 (0.4-718) U/ml at Time point A ($p=0.0153$), 230 (0.4-2,090) U/ml vs. 273.5 (0.4-9,871) U/ml at Time point B ($p=0.1013$), and 179 (0.85-1,749) U/ml vs. 274 (0.4-3,813) U/ml at Time point C ($p=0.2345$) (Figure 8).

Efficacy of BNT162b2 vaccine according to corticosteroid therapy. In patients with corticosteroid therapy ($n=36$) and without corticosteroid therapy ($n=27$), the response rate at the Time point A, B, and C was 30.6% (11/36), 94.4% (34/36) and 97.2% (35/36) in patients with corticosteroid therapy, and 40.7% (11/27), 100% (27/27) and 100% (27/27) in patients without corticosteroid therapy. The median (range) anti-spike protein antibody levels in patients with

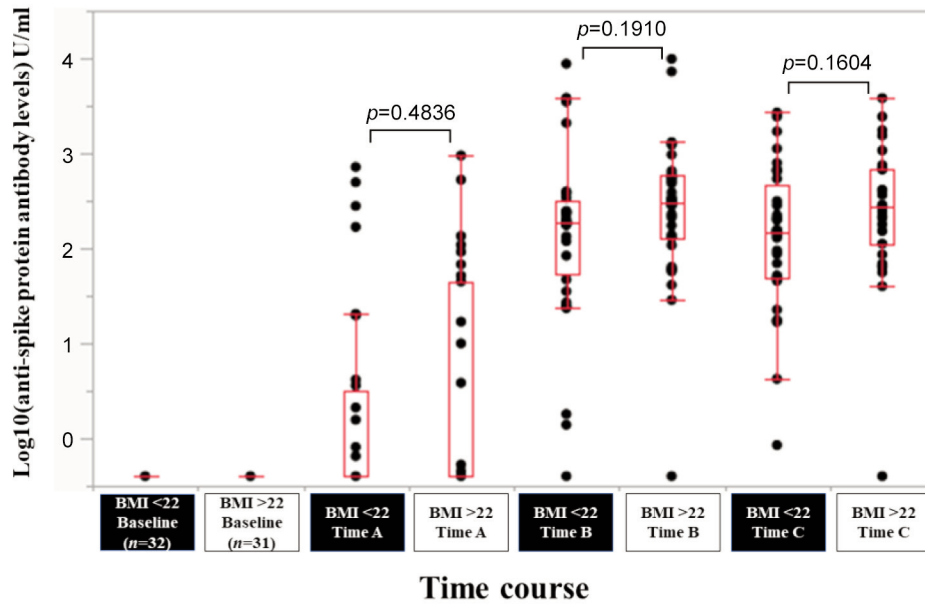


Figure 6. Log10(anti-spike protein antibody levels) U/ml at baseline, Time point A, Time point B, and Time point C according to body mass index (BMI).

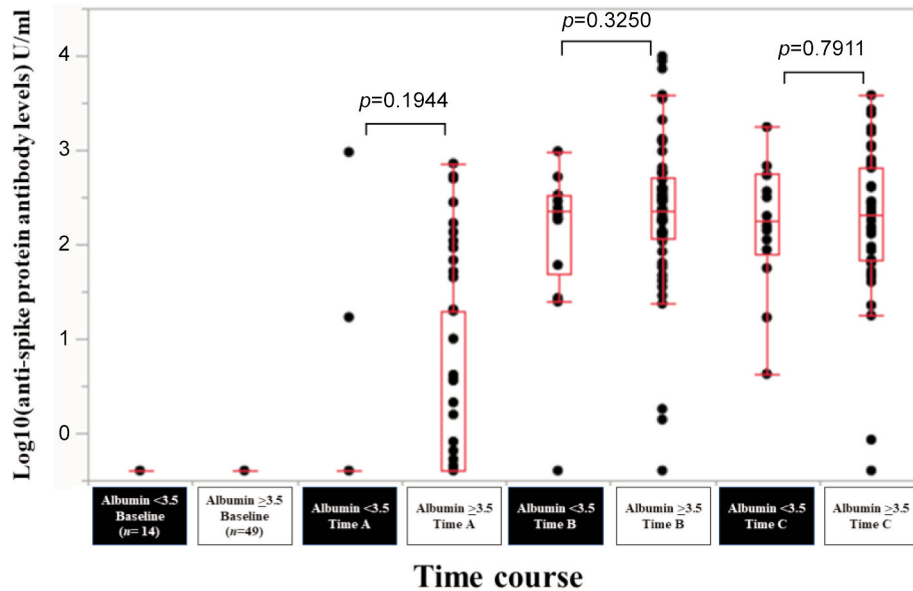


Figure 7. Log10(anti-spike protein antibody levels) U/ml at baseline, Time point A, Time point B, and Time point C according to serum albumin level.

corticosteroid therapy vs. without corticosteroid therapy at the Time point A, B, and C were 0.4 (0.4-527) U/ml vs. 0.4 (0.4-950) U/ml at Time point A ($p=0.8568$), 190.5 (94-9,871) U/ml vs. 247 (23.5-3,489) U/ml at Time point B ($p=0.1198$), and 205 (0.4-3,813) U/ml vs. 206 (17.6-2,436) U/ml at Time point C ($p=0.8241$) (Figure 9).

Efficacy of BNT162b2 vaccine according to ICI therapy. In patients with ICI therapy ($n=7$) and without ICI ($n=56$), the response rate at the Time point A, B, and C was 28.6% (2/7), 100% (7/7) and 100% (7/7) in patients with ICI therapy, and 35.7% (20/56), 96.4% (54/56) and 98.2% (55/56) in patients without ICI therapy. The median (range) anti-spike protein

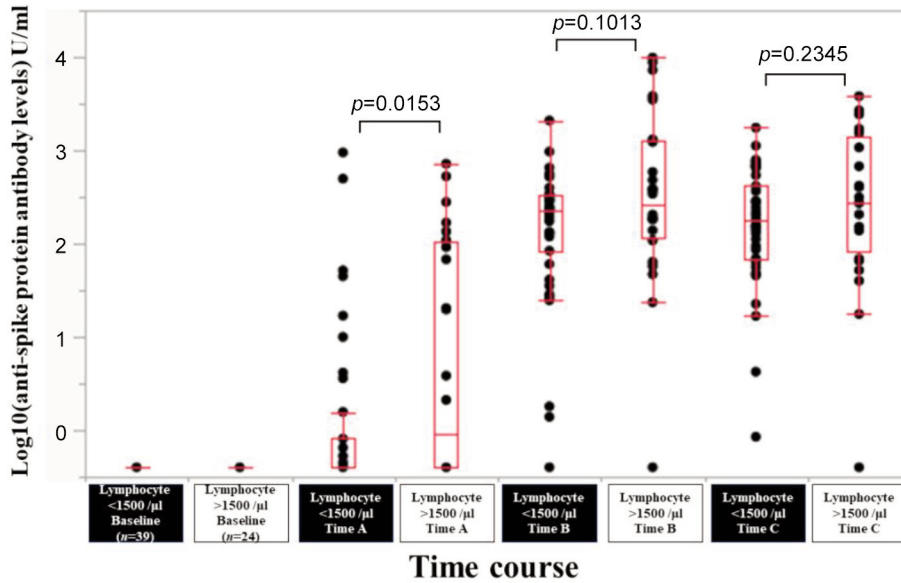


Figure 8. *Log10(anti-spike protein antibody levels) U/ml* at baseline, Time point A, Time point B, and Time point C according to total lymphocyte count.

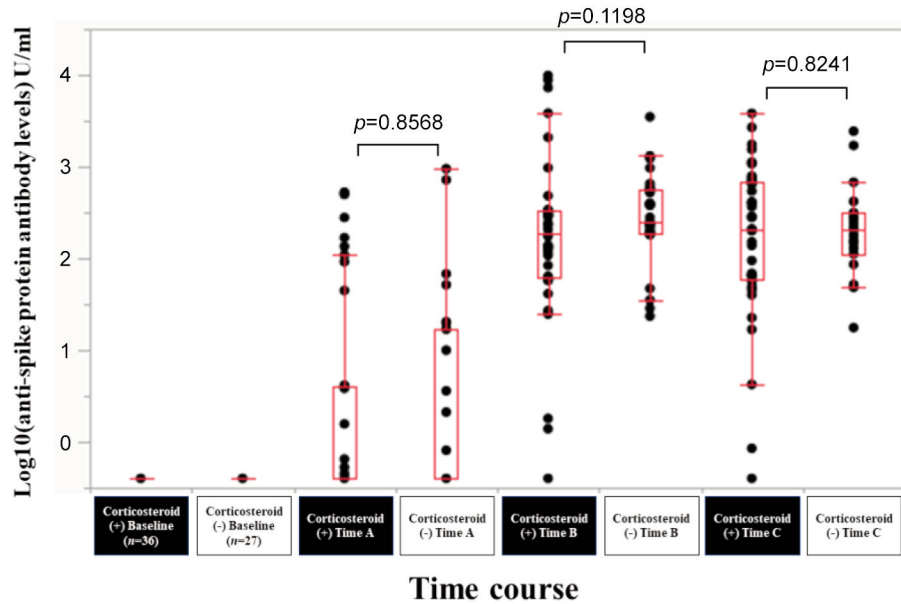


Figure 9. *Log10(anti-spike protein antibody levels) U/ml* at baseline, Time point A, Time point B, and Time point C according to corticosteroid therapy.

antibody levels in patients with ICI vs. without ICI at the Time point A, B, and C were 0.4 (0.4-51.7) U/ml vs. 0.4 (0.4-950) U/ml at Time point A ($p=0.7082$), 230 (27-654) U/ml vs. 231 (0.4-9,871) U/ml at Time point B ($p=0.9827$), and 179 (17.6-245) U/ml vs. 208 (0.4-3,813) U/ml at Time point C ($p=0.6304$) (Figure 10).

Safety profile. At the initial BNT162b2 vaccination, adverse reactions that occurred with a frequency of 10% or greater were local pain (31 cases, 49.2%), fatigue (18 cases, 28.6%), and myalgia (8 cases, 12.7%) (Table II). All adverse reactions improved with symptomatic treatment, and none of the patients required postponement or

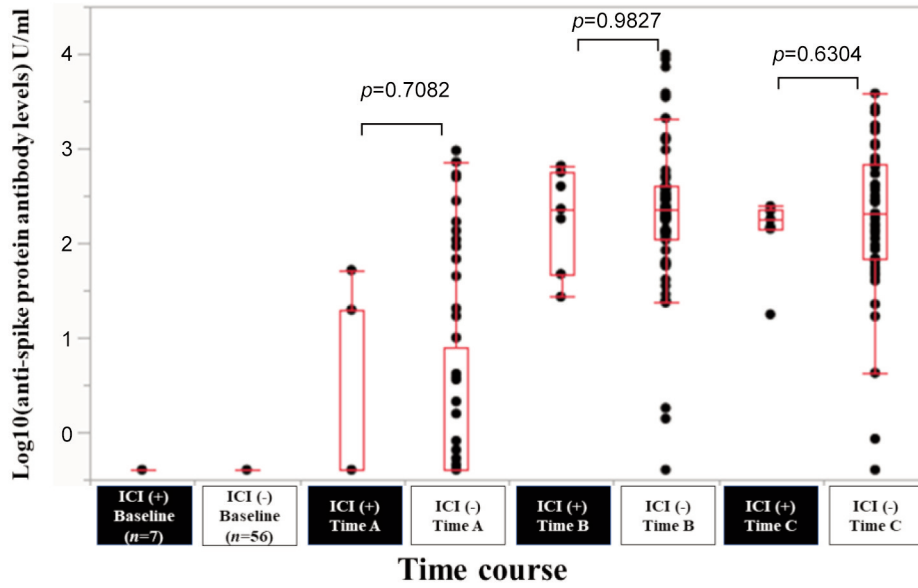


Figure 10. Log10(anti-spike protein antibody levels) U/ml at baseline, Time point A, Time point B, and Time point C according to immune checkpoint inhibitor (ICI) therapy.

discontinuation of systemic chemotherapy because of an adverse reaction.

At the second BNT162b2 vaccination, adverse reactions that occurred with a frequency of 10% or greater were local pain (29 cases, 46.0%), fatigue (23 cases, 36.5%), fever (more than 37.5°C) (15 cases, 23.8%), myalgia (11 cases, 17.5%), headache (9 cases, 14.3%), local swelling (7 cases, 11.1%) and diarrhea (7 cases, 11.1%) (Table II). All adverse reactions improved with symptomatic treatment, and none of the patients required postponement or discontinuation of systemic chemotherapy because of an adverse reaction.

Discussion

In Japan, during the COVID-19 pandemic, the first clinical introduction of the BNT162b2 mRNA vaccine was launched under pressure of time (17, 18). Despite evidence supported by large-scale clinical trials (8, 9), speculation about its safety has been rife and has confused even medical professionals. Under these circumstances, it is essential to disseminate solid evidence on vaccination against COVID-19 infection. Cancer patients are at higher risk of COVID-19 severity and mortality (19, 20). Although Japanese and foreign administrative agencies list cancer patients as a priority group for vaccination, it is unclear whether data from healthy individuals can be extrapolated. On the other hand, it is ethically unacceptable to conduct a randomized controlled trial to test for the efficacy and safety of the COVID-19 vaccine in cancer patients only during the

Table II. BNT162b2 related adverse reaction.

Adverse reaction	First BNT162b2 number (%)	Second BNT162b2 number (%)
Local pain	31 (49.2)	29 (46.0)
Local redness	1 (1.6)	5 (7.9)
Local swelling	3 (4.8)	7 (11.1)
Vertigo	1 (1.6)	4 (6.3)
Dyspnea	1 (1.6)	0 (0)
Fatigue	18 (28.6)	23 (36.5)
Headache	5 (7.9)	9 (14.3)
Chill	2 (3.2)	6 (9.5)
Nausea	4 (6.3)	5 (7.9)
Diarrhea	6 (9.5)	7 (11.1)
Myalgia	8 (12.7)	11 (17.5)
Arthralgia	4 (6.3)	6 (9.5)
Convulsion	1 (1.6)	0 (0)
Fever (more than 37.5°)	2 (3.2)	15 (23.8)

COVID-19 pandemic. In the current study, we focused on immunogenicity. We confirmed the effectiveness of the BNT162b2 vaccine in cancer patients undergoing systemic chemotherapy by following the course of anti-spike protein antibody levels, which are easily measured. As mentioned earlier, sufficient evidence supporting the safety and efficacy of vaccines for cancer patients undergoing systemic chemotherapy is currently lacking (13, 14). Thus, we believe that the current data are worthy of reporting.

The present study was conducted in patients with solid tumors undergoing systemic chemotherapy, and it showed a high response rate (our response rate: 98.4% (62/63) at 3 months after the second BNT162b2 vaccination), which is similar to a previous report on healthy adults (21). In the univariate analyses according to sex, age, ECOG-PS, BMI, serum albumin level, total lymphocyte count, corticosteroid use, and ICI therapy, no significant difference in anti-spike protein antibody levels was found between any two groups at 3 months after the second BNT162b2 vaccination, which indicates the consistent efficacy of BNT162b2 vaccine independent of patient status and tumor status. Although the anti-spike protein antibody levels were lower than those previously reported in healthy adults (10), they were sufficiently high to be effective against COVID-19 (the median anti-spike protein antibody levels in our data: 230 U/ml and 206 U/ml at 1 and 3 months after the second BNT162b2 vaccination). The only patient who did not respond to the BNT162b2 vaccine in this study was a 70-year-old female with ascending colon cancer, a case with no immunological abnormalities or other risk factors. It may be difficult to predict the response to the BNT162b2 vaccine in cancer patients.

It was difficult to obtain sufficient antibody titers in patients with hematologic malignancies undergoing systemic chemotherapy (13, 22, 23). Herishanu *et al*. reported that in 167 patients with chronic lymphocytic leukemia, the antibody response rate of the BNT162b vaccine was 39.5% (22). Perry *et al*. reported that the response rates of the BNT162b vaccine were 49% in patients with B-cell non-Hodgkin lymphoma *vs.* 98.5% in 65 healthy controls (23). This study's results show a higher response rate for patients with solid tumors undergoing chemotherapy than patients with hematological malignancies undergoing multidisciplinary chemotherapy. This may be partly due to the reduced ability to produce anti-spike protein antibodies specific to hematological malignancies and the intensity of chemotherapy (24).

The safety profile of BNT162b in cancer patients undergoing chemotherapy is comparable to previously reported results on healthy adults (8, 9), indicating that BNT162b is effective and safe in Japanese cancer patients undergoing systemic chemotherapy. COVID-19 has not yet subsided, and data on the safety and efficacy of additional vaccinations are essential. We will continue to accumulate data on the BNT162b vaccine in solid cancer patients receiving systemic chemotherapy.

We acknowledge several limitations to the study. First, this is a single-center study. Second, patient backgrounds are highly heterogeneous, involving various kinds of solid malignancies and chemotherapeutic regimens. Third, many patients were excluded from the analysis due to missing data of anti-spike protein antibodies, which also led to bias.

Fourth, it is not clear whether antibody responses in the present study are protective towards COVID-19. Fifth, because the control group (*i.e.*, healthy volunteer) is missing in this study, it is difficult to evaluate whether chemotherapy affected antibody responses. Thus, further studies will be needed to confirm these results.

In conclusion, the BNT162b vaccine in solid cancer patients undergoing systemic chemotherapy is effective and safe. Even in solid cancer patients undergoing systemic chemotherapy, aggressive BNT162b vaccination can be recommended.

Funding

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Conflicts of Interest

None of the Authors has any conflicts of interest to declare.

Authors' Contributions

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