Original Article: Clinical Investigation

Effect of active anticancer therapy on serologic response to SARS-CoV-2 BNT162b2 vaccine in patients with urothelial and renal cell carcinoma

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Abbreviations & Acronyms
AE = adverse event
Ctrl = control
ICI = immune checkpoint inhibitor
IgG = immunoglobulin G
IQR = interquartile range
mRNA = messenger ribonucleic acid
OR = odds ratio
RCC = renal cell carcinoma
SARS-CoV-2 S = severe acute respiratory syndrome coronavirus 2 spike
TKI = tyrosine kinase inhibitor
UC = urothelial carcinoma

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Objectives: To evaluate the serologic response to the BNT162b2 messenger ribonucleic acid vaccine in patients with urothelial carcinoma and renal cell carcinoma.

Methods: Between June 2021 and November 2021, we retrospectively evaluated blood samples from 60 healthy controls (control group), 57 patients with urothelial carcinoma, and 28 patients with renal cell carcinoma who had received two doses of the BNT162b2 vaccine at Hirosaki University Hospital. We determined the immunoglobulin G antibody titers against the severe acute respiratory syndrome coronavirus 2 spike receptor-binding domain. Seropositivity was defined as ≥15 U/mL. We investigate factors associated with antibody titers and seropositivity in the patients with urothelial carcinoma and renal cell carcinoma.

Results: Antibody titers in the control, urothelial carcinoma, and renal cell carcinoma groups were 813, 431, and 500 U/mL, respectively. Seropositivity was 100%, 90%, and 96% in the control, urothelial carcinoma, and renal cell carcinoma groups, respectively. Of the 85 patients, 37 of 57 (65%) and 21 of 28 (75%) were actively undergoing anticancer treatment for urothelial carcinoma and renal cell carcinoma, respectively. Anti-severe acute respiratory syndrome coronavirus 2 spike immunoglobulin G antibody titers and seropositivity was not significantly different between the patients with urothelial carcinoma and renal cell carcinoma. Anti-severe acute respiratory syndrome coronavirus 2 spike immunoglobulin G antibody titers were not significantly associated with active anticancer therapy or steroid treatment for immune-related adverse events. Univariable logistic regression analysis revealed that older age and metastatic disease were significantly and negatively associated with seropositivity.

Conclusions: Patients with urothelial carcinoma or renal cell carcinoma exhibited an adequate antibody response to the BNT162b2 vaccine. Active anticancer therapy was not significantly associated with seropositivity following vaccination with severe acute respiratory syndrome coronavirus 2 BNT162b2 in patients with urothelial carcinoma and renal cell carcinoma.

Key words: mRNA vaccine, renal cell carcinoma, SARS-CoV-2, seropositive, urothelial carcinoma.

Introduction

Patients actively undergoing anticancer therapy are at high risk for impaired serologic response to the SARS-CoV-2 mRNA vaccine.[1–3] Furthermore, the seropositivity rate in patients with solid tumors was reported as slightly lower (approximately 90%) than in healthy controls.[4–6] Systemic chemotherapy and ICIs are two immunoregulation agents frequently administered to patients with advanced UC.[7–12] Treatment with ICIs in combination or ICIs plus TKIs is considered the standard of care for patients with metastatic RCC.[13–18] Furthermore, immune-related AEs are closely associated with high-dose steroid administration in patients treated with ICIs, and steroid use has been associated with impaired humoral response to SARS-CoV-2 mRNA vaccines in patients with cancer.[5,19,20] However, the effect

of different types of anticancer therapy and the concomitant use of steroids on antibody responses to SARS-CoV-2 vaccines in patients with UC and RCC remains unknown. Hence, this single-center study evaluated the serologic response to the BNT162b2 mRNA vaccine in patients with UC and RCC treated with anticancer therapy at an academic hospital in Japan.

Methods

Study design

This retrospective study was approved by the Ethics Committee of Hirosaki University (approval number: 2021-089). Because all participants had previously provided written informed consent for other biomarker studies, the Ethics Committee waived informed consent for our study.

We conducted our study between June 21 and November 1, 2021. The cohort comprised 60 healthy controls (Ctrl group), 57 patients with UC (UC group), and 57 patients with RCC (RCC group) who had received their second dose of the BNT162b2 vaccination at least 7 days before measuring the titer of anti-SARS-CoV-2 antibodies. The Ctrl group included members of the medical staff and medical students at Hirosaki University Hospital. Those with previous SARS-CoV-2 infection or blood samples taken less than 7 days after the second BNT162b2 dose were excluded. Blood samples were collected cross-sectionally and active anticancer treatment was defined at the time of first vaccination. Clinical parameters, such as age, sex, types of anticancer therapy, metastatic disease, and the concomitant use of steroids, were obtained from medical records.

Measurement of anti-SARS-CoV-2 IgG antibody titers

Cross-sectional blood samples collected for regular evaluation were used to measure the titers of IgG antibodies against the SARS-CoV-2 S protein receptor-binding domain using the Elecsys Anti-SARS-CoV-2 S assay (Roche Diagnostics, Meylan, France) on a Cobas 8000/e 801 analytical unit (Roche Diagnostics). According to the manufacturer's data, seropositivity was defined as an anti-SARS-CoV-2 IgG level ≥15 U/mL, which was shown to be sufficient indication of the presence of neutralizing antibodies.

Anticancer treatment

Active anticancer treatment for UC included systemic chemotherapy using gemcitabine plus cisplatin/carboplatin, pembrolizumab, avelumab, durvalumab, and tremelimumab. Active anticancer treatment for RCC included TKIs alone (axitinib and cabozantinib), ICIs plus TKIs (avelumab plus axitinib or pembrolizumab plus axitinib), and ICI combinations (nivolumab plus ipilimumab). We also included post-treatment patients with localized diseases who were not actively undergoing any treatment (off treatment) in the UC ($n = 20$, 35%) and RCC ($n = 7$, 25%) groups.

Outcomes

We evaluated the antibody titers and seropositivity in the Ctrl, UC, and RCC groups as well as in patients with stage M0 and stage M1 disease. We compared the antibody titers and seropositivity between the UC and RCC groups, and patients with stage M0 and stage M1 disease. The effect of different types of anticancer therapies and the concomitant use of steroids on antibody titers and seropositivity rates were compared. We also used univariable logistic regression analysis to investigate the factors associated with seropositivity.

Statistical analysis

Qualitative and quantitative variables were described as numbers with percentages and medians with IQRs, respectively. Chi-squared, Fisher's exact, Mann–Whitney U, and Student t tests were used for statistical comparison between the Ctrl group and the UC and RCC groups. Univariable logistic regression analysis was performed to identify factors associated with anti-SARS-CoV-2 IgG seropositivity after the second SARS-CoV-2 mRNA vaccination dose, and the OR was calculated with a 95% confidence interval. All statistical analyses were performed using BellCurve for Excel v3.10 (Social Survey Research Information Co. Ltd., Tokyo, Japan) and GraphPad Prism v7.00 (GraphPad Software, San Diego, CA, USA). P value of <0.05 was considered as statistically significant.

Results

The background characteristics of the study cohort are summarized in Table 1. Briefly, the median ages were 36 (IQR 27–52), 73 (IQR 70–81), and 72 (IQR 68–77) years in the Ctrl, UC, and RCC groups, respectively. No patient had SARS-CoV-2 infection in this cohort. A blood sample was collected from all participants at a median of 2.9 (IQR 1.7–6.2) months after the first vaccine dose. There were 55 patients with stage M1 disease and 40 with ICI therapy. In the UC and RCC groups, 37 of 57 (65%) and 21 of 28 (75%) patients, respectively, were actively undergoing anticancer therapy, and the remainder in both groups were off treatment. Steroids were administrated to nine patients for immune-related AEs and the dose of steroids was 10 mg or less at the time of vaccination.

A cross-sectional representation of anti-SARS-CoV-2 S IgG antibody titers is shown in Figure 1. After the second BNT162b2 vaccination dose, all participants (100%) in the Ctrl group and 78 of 85 (92%) patients with UC or RCC were seropositive for SARS-CoV-2 S IgG antibodies. The anti-SARS-CoV-2 S IgG antibody titer was not significantly different between the UC (median 431 U/mL) and RCC groups (median 500 U/mL) ($P = 0.334$, Fig. 2a). The seropositivity rate in the UC, and RCC groups was 90%, and 96%, respectively ($P = 0.417$, Fig. 2b). The anti-SARS-CoV-2 S IgG antibody titer did not significantly differ between patients with nonmetastatic disease (M0; median 458 U/mL) and metastatic disease (M1; median 427 U/mL) ($P = 0.319$,

Table 1 Background of participants

|	Ctrl	UC	RCC	P-value†
n	60	57	28	
Age, years (IQR)	36 (27–52)	73 (70–81)	72 (68–77)	0.118
Male, n	26 (43%)	45 (79%)	23 (82%)	0.729
Active anticancer therapy, n		37 (65%)	21 (75%)	0.459
M1 disease, n		33 (58%)	22 (79%)	0.090
ICIs therapy, n		30 (53%)	10 (36%)	0.170
Steroids use		5 (8.8%)	4 (14%)	0.469
Systemic chemotherapy, n		8 (14%)		
TKIs therapy			13 (46%)	
Anti-SARS-CoV-2 S IgG ≥0.8 U/mL, n	60 (100%)	54 (95%)	28 (100%)	
Anti-SARS-CoV-2 S IgG ≥15 U/mL, n	60 (100%)	51 (89%)	27 (96%)	
Median months from first vaccine dose (IQR)	6.4 (5.8–7.0)	2.0 (1.4–3.0)	1.8 (1.4–2.7)	0.159

†UC vs RCC.
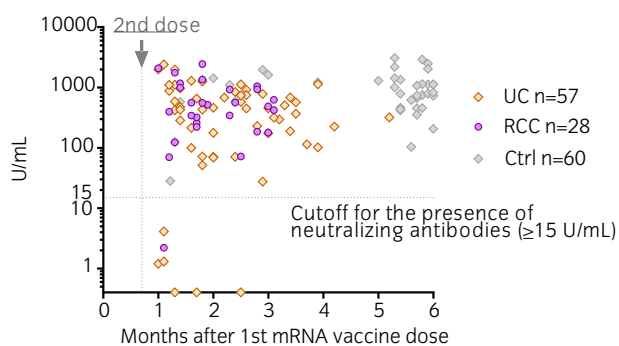
Fig. 1 Cross-sectional evaluation of anti-SARS-CoV-2 IgG S antibody titers. Plot of the anti-SARS-CoV-2 IgG S antibody titers after the first BNT162b2 vaccine dose. Seropositivity was defined as ≥15 U/mL, which was considered to indicate the presence of neutralizing antibodies.

Fig. 2c). The seropositivity rate in the patients with stage M0 and M1 disease was 97% and 89%, respectively ($P = 0.413$, Fig. 2d).

We observed that 92% ($n = 53/58$) of patients undergoing active anticancer therapy were seropositive. The seropositivity rate among the patients with active anticancer therapy in the UC and RCC groups was 87% ($n = 33/37$) and 95% ($n = 20/21$), respectively. In the UC group, the anti-SARS-CoV-2 S IgG antibody titer did not significantly differ between the off-treatment patients (median 458 U/mL) and those receiving ICI therapy (median 369 U/mL) and between the off-treatment patients and those receiving systemic chemotherapy (median 779 U/mL) (Fig. 3a). The seropositivity rate in patients with UC in the ICI therapy, chemotherapy, and off-treatment groups was 87%, 86%, and 95%, respectively (Fig. 3b). In the RCC group, the anti-SARS-CoV-2 S IgG antibody titer did not significantly differ between the off-treatment patients (median 927 U/mL) and those receiving therapy with ICIs ± TKIs (median 369 U/mL) and between the off-treatment patients and those receiving TKIs (median 516 U/mL) (Fig. 3c). The seropositivity rate in patients with UC in the ICIs ± TKI therapy, TKI therapy, and off-treatment groups was 100%, 91%, and 100%, respectively (Fig. 3d). The anti-SARS-CoV-2 S antibody titer in patients with concomitant steroid use (median 72 U/mL) was significantly lower than those without concomitant steroid use (median 480 U/mL) ($P = 0.014$, Fig. 3e). The seropositivity rate in patients with steroids (−) and steroids (+) was 92% and 89%, respectively ($P = 0.557$, Fig. 3f). The seropositivity rate in patients with concomitant steroid use in the UC and RCC groups was 89% and 96%, respectively (Fig. 3f). We evaluated the effect of prior therapy on anti-SARS-CoV-2 S IgG antibody titer in UC patients who are treated with ICI ($n = 30$) (Fig. S1a). The seropositivity in patients with ICI ≤2 lines ($n = 28$) and ≥3 lines ($n = 2$) was 89% and 50%, respectively (Fig. S1b). We observed no significant association between the time anti-SARS-CoV-2 S IgG antibody titer and time from final administration of chemotherapy to initiation of ICIs therapy (Fig. S1), time from final administration of chemotherapy to vaccination (Fig. S1d), and time from initiation of ICIs therapy to vaccination (Fig. S1e).

Univariable logistic regression analysis for seropositivity showed that age (OR 0.92; $P = 0.045$) and stage M1 disease (OR 0.09; $P = 0.029$) were significantly and negatively associated with seropositivity (Table 2). Summary of the present study was shown in a visual abstract (Fig. S2).

Discussion

The effect of active anticancer treatment on the serologic response to the SARS-CoV-2 mRNA vaccine is a subject of intense interest. Several previous studies showed that patients treated for solid tumors have shown an impaired but sufficiently maintained serologic response (90–95.2%) after receiving the second BNT162b2 dose.[5,20] Our observation of seropositivity in patients with UC and RCC is consistent with previous studies.[4–6] However, the response of patients with UC and RCC who were receiving therapy with ICIs and/or TKIs remains unreported. Our study revealed that most of the patients with UC and RCC exhibited an adequate antibody response (90–96%) to the BNT162b2 vaccine, but nonresponders were widely distributed among patients with UC. This observation might be influenced by the older age in the UC group (median 73 years). Although the concomitant use of steroids significantly impacted the titer of
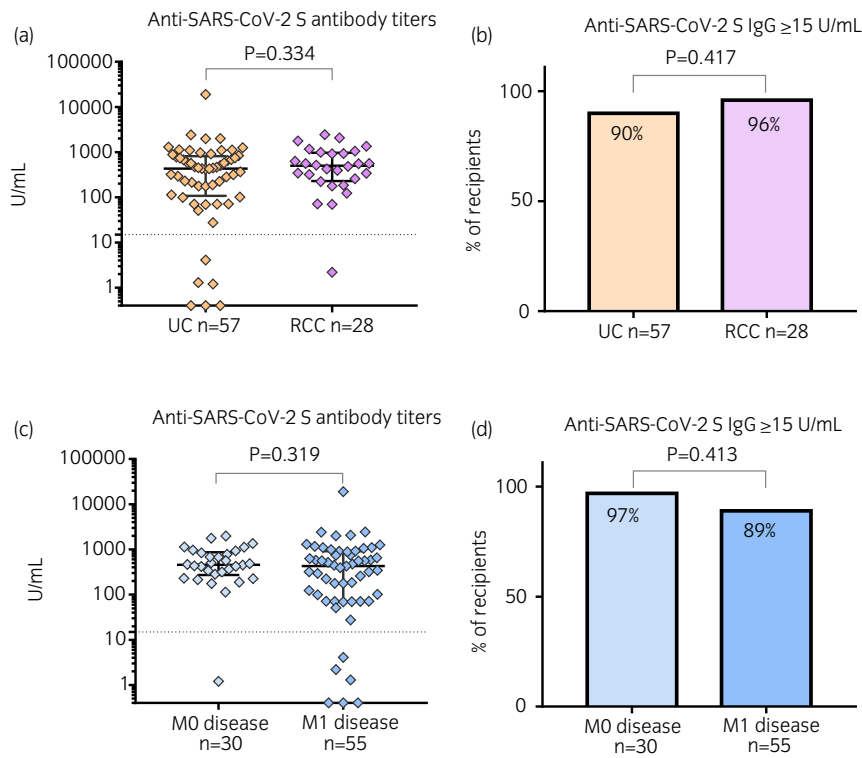
Fig. 2 Comparison of anti-SARS-CoV-2 IgG S antibody titers and seropositivity among the Ctrl, UC, and RCC groups. (a) Comparison of antibody titers between patients with UC and RCC. (b) Seropositivity in patients with UC, and patients with RCC. (c) Comparison of antibody titers between patients with nonmetastatic (M0) and metastatic (M1) disease. (d) Seropositivity in patients with M0 and M1 disease.
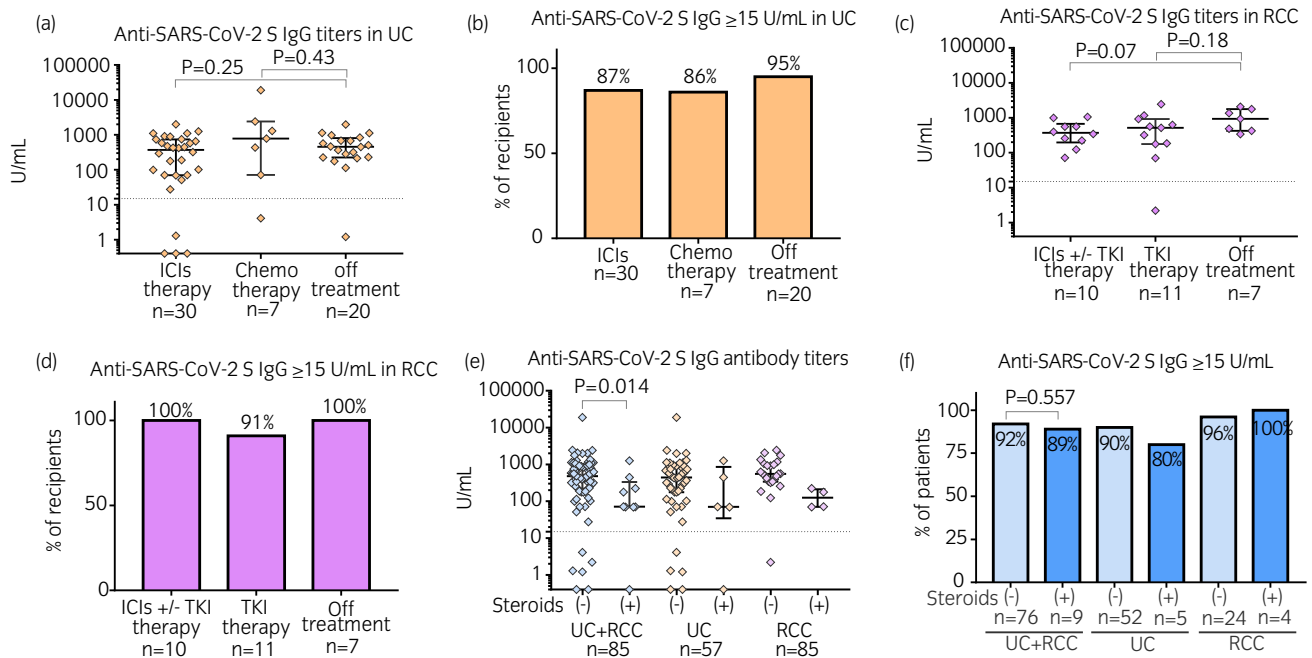

Fig. 3 Comparison of anti-SARS-CoV-2 IgG S antibody titers and seropositivity between patients undergoing active cancer therapy and off-treatment patients with UC or RCC. (a) Comparison of antibody titers between off-treatment patients with UC and patients with UC receiving ICIs or systemic chemotherapy. (b) Seropositivity in off-treatment patients with UC and patients with UC receiving ICIs or systemic chemotherapy. (c) Comparison of antibody titers between off-treatment patients with RCC and patients with RCC receiving ICIs ± TKIs or TKI therapy. (d) Seropositivity in off-treatment patients with RCC and patients with RCC receiving therapy with ICIs ± TKIs or TKIs only. (e) Comparison of antibody titers between patients with steroids (−) and steroids (+) in all patients, UC patients, and RCC patients. (f) Seropositivity in patients with steroids (−) and steroids (+).

antibodies to the SARS-CoV-2 vaccine, it was not associated with seropositivity. This finding might be related to the minimum dose of steroids (prednisone: 5–10 mg) in our cohort.

Although further study is necessary, a minimal dose of steroids may not impair seropositivity to the SARS-CoV-2 mRNA vaccination.

Table 2 Univariable logistic regression analysis for seropositivity

Variables	Factor	*P*-value	OR	95% confidence interval
Age	Continuous	0.045	0.92	0.84–1.00
Sex	Male	0.262	0.29	0.03–2.51
Disease status	M1 disease	0.029	0.09	0.01–0.78
ICIs therapy	Yes	0.092	0.26	0.06–1.24
Steroids	Yes	0.382	0.37	0.04–3.45
TKIs	Yes	0.618	0.57	0.06–5.15
Chemotherapy	Yes	0.322	0.32	0.03–3.04

Our univariable analysis revealed that older age and M1 disease, not active anticancer therapy, were significantly associated with impaired seropositivity. Older age is a well-known risk factor for impaired serologic response to vaccinations. Furthermore, impaired serologic response in patients with M1 disease is reasonable in terms of cancer development in the context of an immunosuppressed state. Therefore, it must be recognized that not only active treatment interventions but also older age and metastatic status are key factors involved in impaired serologic response to the BNT162b2 vaccine.

Although we observed that 92% (*n* = 53/58) of patients undergoing active anticancer therapy were seropositive, the effectiveness of SARS-CoV-2 vaccines cannot be solely measured according to antibody titers.[21] Both antibody and T cell responses are necessary to protect against infection. Although a very low antibody response rate (17.8%) was reported in immunocompromised kidney transplant recipients after the second mRNA vaccination dose, the induction of an anti-S T cell-specific response was observed in 51.1% of these patients after the second mRNA vaccination dose.[22] These observations suggested that the positive response rate for cellular immunity might differ from the antibody titer, meaning that the evaluation of T cell response in individuals with impaired immunogenicity is crucial. Thus, it must be recognized that several issues still remain unknown regarding the level of antibodies necessary to protect against SARS-CoV-2 infection.

The seropositivity rates in patients with UC and RCC in our study are similar to that in previous studies of patients with solid tumors (approximately 90%).[4–6] However, the definition of anti-SARS-CoV-2 IgG seropositivity varied across these studies because of differences in the study population, sample size, and measurement methods. There are several commercially available kits that measure the titer of anti-SARS-CoV-2 IgG antibodies, and the many antibody testing methods and different cutoff values employed across the studies may affect the results. For example, the LIAISON SARS-CoV-2 TrimetricS IgG assay (Diasorin, Saluggia, Italy) uses a positive cutoff value of 13.0 arbitrary U/mL,[23,24] the Anti-SARS-CoV-2 QuantiVac ELISA (IgG) for S protein (Euroimmun, Lübeck, Germany) uses a positive cutoff value of 35.2 binding antibody U/mL,[25] the ARCHITECT SARS-CoV-2 IgG II Quant assay for S protein (Abbott Laboratories, Chicago, IL, USA) uses a positive cutoff value of 50.0

arbitrary U/mL,[26,27] and the Elecsys Anti-SARS-CoV-2 S assay (Roche Diagnostics) uses a positive cutoff value of ≥15 U/mL for the presence of neutralizing antibodies. Currently, only one study has investigated the agreement of three serologic tests from different suppliers (Abbott, Roche, and Diasorin),[28] and a good agreement (Cohen kappa, 0.71–0.87) was reported. However, the same study also reported the inadequate performance of these tests with samples with low seroprevalence.[28] Thus, these findings highlight the importance of carefully interpreting the results from different tests. Information concerning the activity levels necessary to protect against breakthrough infections is also needed.

The major limitations of our study include the limited sample size in a single-center and retrospective design. We could not compare the antibody titers between the Ctrl and UC/RCC groups because of the age difference. The duration of long-term immunity remains unclear because we evaluated IgG antibody titers during the early phase of mass immunization in Japan. Because the acquisition of cellular immunity is necessary for infection protection, the measurement of antibody titers alone cannot adequately assess the immune response to vaccination. Furthermore, the efficacy of Pfizer/BioNTech BNT162b2 for the Omicron variant is limited because it can escape antibody neutralization.[29] The Omicron variant is rapidly becoming the dominant SARS-CoV-2 virus, which limits the usefulness of the present study.

In conclusion, this retrospective study confirmed that undergoing active anticancer therapy did not greatly reduce the rate of anti-SARS-CoV-2 IgG seroconversion after the second BNT162b2 mRNA vaccine in patients with UC or RCC. However, several questions remain unanswered, and further investigation is warranted to determine the duration of immunity under active anticancer therapy, the effect of reduced titers on the protective activity against breakthrough infections, and the efficacy of a third vaccination dose in patients with UC or RCC with an impaired serologic response.

Acknowledgments

Author contributions

Kyo Togashi: Data curation; writing – review and editing. Shingo Hatakeyama: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; visualization; writing – original draft; writing – review and editing. Tohru Yoneyama: Conceptualization; data curation; formal analysis; funding acquisition; methodology; software; writing – review and editing. Tomoko Hamaya: Data curation; methodology; writing – review and editing. Takuma Narita: Data curation; resources; writing – review and editing. Naoki Fujita: Data curation; methodology; resources; writing – review and

editing. Hiromichi Iwamura: Data curation; methodology; writing – review and editing. Teppei Okamoto: Data curation; methodology; resources; writing – review and editing. Hayato Yamamoto: Data curation; methodology; resources. Takahiro Yoneyama: Data curation; methodology; resources; supervision. Yasuhiro Hashimoto: Data curation; methodology; resources; supervision. Chikara Ohyama: Conceptualization; data curation; funding acquisition; project administration; resources; supervision.

Conflict of interest

None declared.

Approval of the research protocol by an Institutional Reviewer Board

Yes (2021–089).

Informed consent

Obtained via an opt-out approach.

Registry and the Registration No. of the study/trial

N/A.

Animal studies

N/A.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. The effect of prior therapy on anti-SARS-CoV-2 S IgG antibody titer in UC patients who are treated with ICI (*n* = 30). (a) Schema of analysis. (b) The effect of accumulation of treatment (treatment lines) on humoral response

between the patients with ICI ≤2 lines (*n* = 28) and ≥3 lines (*n* = 2). (c) The association between the anti-SARS-CoV-2 S IgG antibody titer and time from final administration of chemotherapy to initiation of ICIs therapy. (d) The association between the anti-SARS-CoV-2 S IgG antibody titer and

time from final administration of chemotherapy to vaccination. (e) The association between the anti-SARS-CoV-2 S IgG antibody titer and time from initiation of ICIs therapy to vaccination.

Figure S2. Visual abstract.

Editorial Comment

Editorial Comment from Dr Kobayashi to Effect of active anticancer therapy on serologic response to SARS-CoV-2 BNT162b2 vaccine in patients with urothelial and renal cell carcinoma

In this issue of *International Journal of Urology*, Togashi *et al.*[1] reported the efficacy of vaccination for SARS-CoV-2 with BNT162b2 in patients with urothelial cancer (UC) and renal cell cancer (RCC) by evaluating post-vaccination seropositivity. The study demonstrated that humoral response, defined as an anti-SARS-CoV-2 IgG level ≥15 U/mL according to the manufacturer's data, was ≥90% among these patients. Although high, this proportion is considerably lower than the 99% to 100% found in control groups.[1–3] Indeed, the post-vaccination seropositivity in UC and RCC patients altogether was 91.8% (78 of 85), which was significantly lower than that in the control groups (*P* = 0.0415, Fisher's exact test).

It seems to be at least partly attributed to the significant difference in age between control group and the patients, as is often the case in such studies.[2] It should be also noted that the present study evaluated seropositivity after the second dose of BNT162b2. A previous report demonstrated that antibody levels increased significantly after the third booster dose, irrespective of active anticancer therapy being ongoing or not.[4] The authors may be able to evaluate antibody levels in their patients and controls after the booster doses.

As the authors also mentioned, there are a lot more to be answered in the future studies. How long will the antibody titers once established be maintained? Does tumor burden or anticancer therapy affect it? These data will be important when considering the optimal intervals for booster doses in patients on cancer treatment. Does tumor burden, metastatic site, or modality and intensity of anticancer therapy affect the susceptibilities to vaccine side effect, virus infection, aggravation, or mortality? Does vaccination itself affect treatment response, adverse treatment events, and prognosis of cancer patients? Considering that systemic immunological condition may substantially affect both SARS-CoV-2 vaccination and treatment outcome of UC/RCC patients and vice versa,[5]

clinical significance of SARS-CoV-2 vaccination in cancer patients should be further studied.

Despite these unanswered questions, the authors should be congratulated for their timely report on the efficacy of SARS-CoV-2 vaccine in Japanese patients with UC or RCC. Further reports will be warranted in the future.

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Conflict of interest

None declared.

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