Immunogenicity of ChAdOx1-nCoV-19 vaccine in solid malignancy patients by treatment regimen versus healthy controls: A prospective, multicenter observational study

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Summary

Background Limited data exists regarding the efficacy of ChAdOx1-nCoV-19 vaccine against Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in solid cancer patients. We aimed to assess the immunogenicity of the ChAdOx1-nCoV-19 vaccine and the impact of different anticancer therapies for solid malignancies on immune response.

Methods This prospective, longitudinal observational study of immunogenicity following ChAdOx1-nCoV-19 vaccination among 385 solid cancer patients on active cancer treatment was conducted in two oncology centers. Participants received the first dose between June 18 and July 27, 2021 and the second dose at 8-10 weeks later. Blood samples were evaluated for total immunoglobulins against the receptor-binding of SARS-CoV-2 spike protein (anti-RBD total-Ig) before, and 4-week after the first- and second-doses. The primary endpoint was the geometric mean titers (GMT) of antibody among solid cancer patients compared to healthy controls and the impact of different cancer treatment types.

Findings Among solid cancer patients, the antibody level increased more slowly to significantly lower levels than achieved in healthy controls. The GMT at 4-weeks post-vaccination in cancer vs. healthy were 224.5 U/ml (95%CI 176.4–285.6) vs. 877.1 U/ml (95%CI 763.5–1008), $p<0.0001$), respectively. For different types of cancer treatments, chemotherapy agents, especially anthracyclines (GMR 0.004; 95%CI 0.002–0.008), paclitaxel (GMR 0.268; 95%CI 0.123–0.581), oxaliplatin (GMR 0.340; 95%CI 0.165–0.484), and immunotherapy (GMR 0.203; 95%CI 0.109–0.381) showed significantly lower antibody response. Anti-HER2, endocrine therapy and 5-fluouracil or gemcitabine, however, had less impact on the immune response.

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Interpretation Suboptimal and heterogeneous immunologic responses were observed in cancer patients being treated with different systemic treatments. Immunotherapy or chemotherapy significantly suppressed the antibody response.

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Keywords: ChAdOx1-nCoV-19 vaccine; Immunogenicity; Cancer patients; Cancer treatments

Research in context

Evidence before this study

Patients with cancer are at high risk for severe coronavirus disease 2019 (COVID-19) disease, vaccination is recommended for all, regardless of cancer treatment. Nonetheless, the SARS-CoV2 vaccine efficacy and safety was initially uncertained in cancer patients. In April 2021, Monin, L. et al. firstly reported significantly lower seroconversion rates after first dose of BNT162b2 vaccine in cancer patients. Subsequent reports supported lower immunogenicity to mRNA in cancer patients, as compared to healthy control.

ChAdOx1-nCoV-19 (AZD1222), adenoviral vector vaccine, is commonly used worldwide but United State. Since vaccine efficacy and safety of ChAdOx1-nCoV-19 in cancer patients have not been reported before this study initiation.

Added value of this study

Similar to previous reports of mRNA vaccine efficacy, antibody response to ChAdOx1-nCoV-19 COVID-19 vaccination in cancer patients rose more slowly, ultimately reaching significantly lower levels compared to healthy adults. Additionally, suboptimal and heterogeneity of antibody response after ChAdOx1-nCoV-19 COVID-19 vaccination was influenced by types of treatment that cancer patients received. Antibody responses were attenuated in patients received immunotherapy, tyrosine kinase inhibitors or chemotherapy-containing treatment, but not in those received anti-HER2 or endocrine therapy. Different cytotoxic agent regimens also differently affected immunogenicity against SARS-CoV-2.

Implications of all the available evidence

The primary results supported the modification of SARS-CoV2 vaccine program for cancer patients with active treatment from usual program for general population. Post-vaccination antibody measurement could be used to monitor adequate immune responses in these vulnerable patients, and additional doses of COVID-19 immunization should be offered to increase protection against COVID-19 disease. Other preventive measures including the use of masks, physical distancing measures and sanitizer are still critical in vaccinated patients with cancer. Effect of different cancer treatments to SARS-CoV2 vaccine efficacy should be more explored especially immunotherapy and different cytotoxic chemotherapy.

Introduction

Cancer patients have a greater risk of adverse outcomes from Coronavirus disease 2019 (COVID-19) infection.[1,2] Consequently, COVID-19 vaccination is recommended in all cancer patients regardless of cancer treatment[3], but data describing how immunogenicity is modified in oncology patients is limited because patients with serious comorbidities are excluded from registration trials, and a relatively short period of post-vaccine marketing use.[4,5]

Previous studies have reported diminished immune responses after COVID-19 vaccine in subsets of solid cancer patients undergoing active cancer therapy.[6,7] However, others found adequate immune response in patients receiving either chemotherapy, immunotherapy, or chemoimmunotherapy.[8] Most of these studies were performed in Europe and USA, where vaccination programs relied predominantly on mRNA COVID-19 vaccines including the BNT162b2 and mRNA-1273, and data describing immunogenicity to the viral-vectored vaccine ChAdOx1-nCoV-19 in sole tumor patients are scarce. Moreover, no studies have assessed immunogenicity by the key components in treatment regimens.

In Thailand, most cancer patients were immunized with the ChAdOx1-nCoV-19 vaccine during the early phase of the vaccination program prioritizing for vulnerable groups (beginning June 2021). Previous evidence from healthy adults suggests that the efficacy of ChAdOx1-nCoV-19[5] was slightly lower versus the mRNA platform (70% vs 94%).[4,9,10] Therefore whether regarding adequate immune responses are elicited in

these cancer patients in unclear, particularly in those concurrently receiving systemic treatment which could modify immune responses.

To determine whether optimal protection is reached for these vulnerable patients, we launched a prospective multicenter study investigating immunogenicity and safety following ChAdOx1-nCoV-19 vaccination in solid cancer patients who were actively receiving cancer treatment. Here, we report the primary outcome of anti-SARS-CoV-2 antibody concentrations after a complete two-dose course of ChAdOx1-nCoV-19 vaccines, 8-10 weeks apart, compared to a group of healthy adults.

Methods

Study design and participants

This prospective, longitudinal cohort study was performed at two academic cancer centers in Thailand: (1) King Chulalongkorn Memorial Hospital and Chulalongkorn University (CU) and (2) Phrapokklao Hospital (PPK). Between June 18 and July 27, 2021, solid cancer patients aged ≥18 years and actively receiving cancer treatments were enrolled, irrespective of cancer type or stage. Treatment was categorized based on the type given in the 4-weeks before the first vaccine dose. Exclusion criteria were previous history of SARS-CoV-2 infection and life expectancy less than six months. Patients were immunized with two doses of ChAdOx1-nCoV-19 vaccines, administered with an interval of 8-10 weeks. Blood samples were collected at five timepoints: before first dose (TP1), 4-week post-first-dose (TP2), before second dose (TP3), 4-week post-second dose (TP4) and 12-week post-second dose (TP5), (Supplemental figure S1). The outcome was SARS-CoV2 antibody concentration at 4-weeks after the second vaccine dose and safety. Local and systemic adverse events were graded according to FDA's toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials.[11] Adverse events were recorded for seven days after injection using self-administered online and paper questionnaires. Post-hoc analysis included surrogate neutralization of the SARS-CoV-2 wild-type strain and the B.1.617.2 variant of concern (Delta) in a subset of 91 samples.

All patients provided written informed consent and this cohort study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University (No. 486/64) and the Chanthaburi Research Ethics Committee/Region 6 (CTIREC) (No. 044/64).

Comparison with healthy individuals

One-hundred and seventy healthy adults who received the ChAdOx1-nCoV-19 vaccine at two Thai sites (AS and RA), from two sites recruited from March and June 2021 and previously published,[12] were used as a control comparison group. The AS cohort comprised 90 healthy individuals vaccinated with two-doses of ChAdOx1-nCoV-19 vaccine administered 10 weeks apart. Serological immune responses were evaluated before pre-prime vaccine (TP1), pre-boost vaccine (TP3), and 4-week post-second-vaccine (TP4). Thirty-five healthy individuals were additionally assessed 4-week post first vaccine (TP2) after a protocol amendment. For the RA cohort, 80 healthy adults received two-doses of ChAdOx1-nCoV-19 vaccine administered 10 weeks apart. The immune responses 4-week post-second vaccine was evaluated in 169 healthy adults, 1 participant who did not receive the second dose due to an adverse event was excluded. The study in healthy controls was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University (No. 192/64).

Serological assessment

Serum samples were tested for total immunoglobulins (Ig) specific to the receptor-binding domain (RBD) of the SARS-CoV-2 spike (S) protein (anti-RBD total Ig) using Elecsys SARS-CoV-2 S assay according to the manufacturer's instruction (Roche Diagnostics, Basel, Switzerland). The assay's detection limit is 0.4 U/mL and antibody concentrations ≥0.8 U/mL are considered positive.

Given the availability of surrogate neutralization test and emerging strain of concern after study initiation, we ran an ad hoc neutralization test against the SARS-CoV-2 wild-type strain and the variant of concern B.1.617.2 (Delta) using cPass SAR-CoV-2 neutralizing antibody detection kit (GenScript, Piscataway, NJ, USA) in a random subset of samples (91 and 36 from the cancer and healthy cohorts, respectively). This ELISA-based surrogate virus neutralization test (sVNT) allows indirect detection of potential neutralizing antibody by testing for antibody-mediated inhibition of SARS-CoV-2 RBD binding to the human receptor angiotensin converting enzyme 2 (ACE2). The recombinant RBD of Delta variant contains L452R and T478K mutations. Briefly, the serum samples were diluted 1:10 with buffer and incubated with RBD conjugated to horseradish peroxidase for 30 min. at 37 °C. Next, 100 µL of the sample mixture was added to a capture plate pre-coated with human ACE2 and incubated for 15 minutes at 37 °C. After washing, 100 µL of TMB chromogen solution was added and the plate incubated in the dark for 15 min at room temperature. After the addition of 50 µL stop solution, samples were read at 450 nm. The ability of a serum to inhibit binding between RBD and ACE2 was calculated as follows: 1 - (average OD of sample/average OD of negative control), multiplied by 100. Inhibition of ≥30% was considered positive.

Statistical analysis

Patients who received at least one dose of the ChAdOx1-nCoV-19 vaccine who were seronegative for baseline anti-RBD total Ig, and had at least 1 additional immune response assessment, were included in the analysis. Patients who developed SARS-CoV-2 infections during follow-up had their data excluded from the analysis thereafter. Anti-RBD total Ig levels were reported as geometrical mean titers (GMT) with 95% confidence interval (CI). Percentage of surrogate neutralization was presented as median with interquartile range (IQR). The nonparametric Mann-Whitney and Kruskal-Wallis test followed by Dunnett's multiple comparisons test was used to compare anti-RBD total Ig levels between two independent groups and three or more groups, respectively. Correlation between anti-RBD total Ig and surrogate neutralization was assessed by Spearman's correlation.

The GMT ratio (GMR) was calculated using linear regression with an outcome of log transformed antibody titre post vaccination (TP4), versus the health controls as a reference. Adjustment was made for sex and age. Coefficients and 95%CI were then back transformed.

Statistical analysis was done using GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA), Stata 15 (Statacorp LLC, College Station, TX), and SPSS Statistics version 28.0 (IBM Corp., Armonk, NY). Two-sided p values level <0.05 were considered statistically significant.

Role of the funding sources

The funders had no role in study design, data collection, analysis and interpretation, decision to publish, or preparation of the manuscript. SL, NT, NP, PS and PW had access directly data and ST, SL, NT had final responsibility for decision to submit the manuscript for publication.

Results

Cohort characteristics and vaccination

Between June 18 and July 27, 2021, 399 solid cancer patients on active cancer treatment were recruited for the study (Figure 1). At data cutoff on December 10, 2021, the median follow-up was 158 days (Interquartile range (IQR), 151–164). After exclusion of 6 patients who acquired SARS-CoV-2 infections and 8 patients with insufficient follow-up to antibody assessment, 385 participants were included in the primary immunogenicity analysis. Of these, 367/385 (95%) received the second ChAdOx1-nCoV-19 vaccine, a median of 59.5 (56–70) days after the first dose. Five percent of patients (18 of 385) did not receive the second dose due to either cancer-related deaths (*n*=5), SARS-CoV infections (*n*=4), study withdrawal (*n*=6) or illness (*n*=1). The median time from the second vaccine administration to blood collection for the primary endpoint was 28 (IQR 28-28, min–max 21–51) days (Figure 1).

The median age of solid tumor patients was 60 (IQR 50–68) years, and 62% were female. Most patients were diagnosed with breast cancers (*n*=116, 30%), lung cancers (*n*=98, 25.5%), and colorectal cancers (*n*=73, 19%). Types of cancer treatment given within 4 weeks of the first dose included chemotherapy (CMT)-containing regimens (*n*=206, 54%), tyrosine kinase inhibitors (TKI) (*n*=92, 24%), immunotherapy (IO)-containing regimens (*n*=35, 9%) and cyclin-dependent kinase inhibitors (CDKi) (*n*=18, 4.7%), endocrine therapy (*n*=14, 3.6%), and anti-human epidermal growth factor receptor 2 therapy (anti-HER2) (*n*=13, 3.4%). Most patients had advanced disease, 44% (168/385) with de-novo metastasis and 22.3% (86/385) with recurrent disease. During vaccination, 49% (189/385) of patients received corticosteroids, mostly for pre-medication purpose (47.5%, 183/385) and only 1.6% (6/385) for therapeutic aims (equivalent of >10 mg prednisolone ≥ 1 week) either as a part of therapeutic regimen for prostate cancer, reduction brain edema during whole brain radiation, or treatment of immunotherapy-induced secondary adrenal insufficiency. Fifty-three percent of cancer patients had no previous medical conditions, whereas 106 patients (27.5%), 57 patients (14.8%) and 57 patients (14.8%) had hypertension, diabetes and dyslipidemia, respectively (Table 1). Of 169 healthy volunteers, who received two ChAdOx1-nCoV-19 vaccine doses, the median age was 47 (IQR 36.5–60) years and 58% were female as previously described.[12]

RBD-specific SARS-CoV-2 antibody response to the ChAdOx1-nCoV-19 vaccines

Following the ChAdOx1-nCoV-19 vaccine, levels of anti-RBD total Ig in solid cancer patients rose more slowly, and to significant lower titers than those of healthy controls at every follow-up time-points (TP2-TP4, $p<0.001$) (Figure 2). The GMT of anti-RBD total Ig at TP2, TP3 and TP4 were 3.4 (95%CI 2.8–4.2), 10.7 (95%CI 8.6–13.3), and 224.5 (95%CI 176.4–285.6) U/mL in patients with solid tumors vs. 51.0 (95%CI 32.1-81.2), 68.1 (95%CI 53.7–86.4), 877.1 (95%CI 763.5–1008) U/mL in healthy controls. The seroconversion rate following the first vaccine was 60.8% (95%CI 55.7–65.7) in oncology patients compared with 97.1% (95%CI 84.7–99.9) in healthy controls. Although the seroconversion rate in the oncology group increased to 93.6% (95%CI 90.5–96) after the second dose (vs 100% (95%CI 97.8–100) in controls), the GMT titers of anti-RBD total Ig were 4-fold lower than controls, with the GMT ratio (GMR) of 0.25 (95%CI 0.17–0.37) after adjustment for sex and age. In addition, to address the potential confounding effect of age difference between cancer and heathy cohort, age-matched ad-hoc analyses

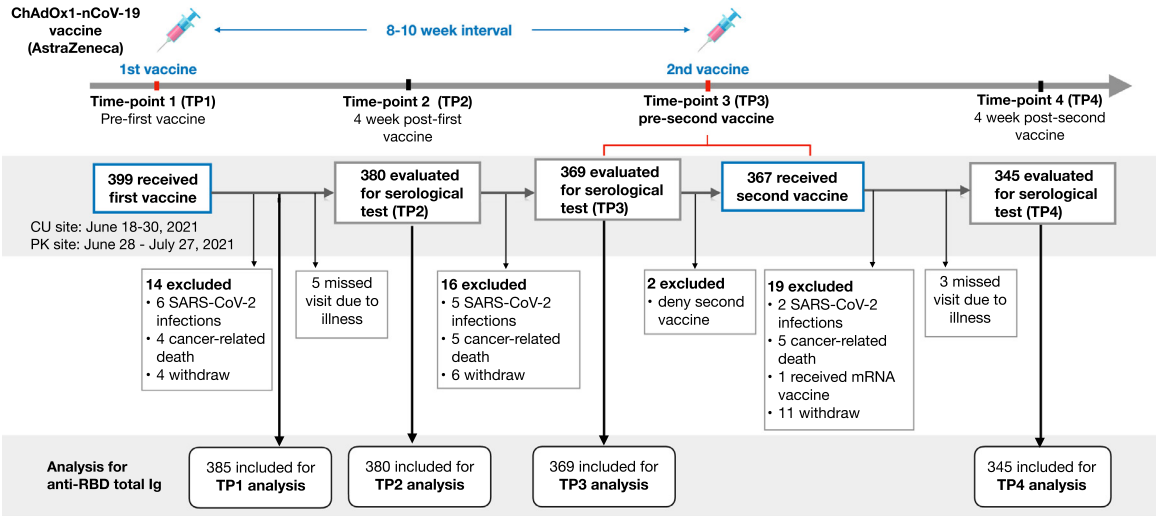

Figure 1. Study flow diagram of the cancer cohort.

in a subgroup of patients (n=114 for each cohort with median age of 53 years) were performed (Figure S5). The anti-RBD antibody levels in cancer patients were significantly lower than healthy controls ($p<0.0001$, GMT 258.8 (95%CI 175–382.8) U/mL in cancer patients vs 858.7 (95%CI 725.9–1016) U/mL in healthy controls). Seroconversion rates 4 and 8–10 weeks after the first dose, and 4 weeks after the second dose, by cancer type and treatment are shown in table S2 and clinical characteristics of 24 patients who were seronegative after complete vaccination were showed in Table S4. It was noted that 62.5% (15/24) of seronegative patients received anthracycline-containing regimens.

Impact of different treatments types on immunogenicity

All cancer patients were on active cancer treatment within a 4-week window prior to the first vaccination., and antibody responses differed according to the type of treatment given. Following two-dose vaccination, patients who received either immunotherapy (GMT 145.2 U/mL, 95%CI 70.2–298.1) or chemotherapy-containing regimens (GMT 159.0 U/mL, 95%CI 107.3 –235.6) or TKI (GMT 364.8 U/mL, 95%CI 274.5–485) had significantly lower antibody responses than healthy controls. While the treatment with endocrine therapy, anti-HER2 or CDKi had minimal impact on antibody responses compared to controls (Figure 3a).

Because of the wide range of antibody responses observed in this mixed group of patients receiving various cytotoxic chemotherapy regimens, and since different chemotherapeutic agents have different immunosuppressive effects, we further explored the impact of different drug classes on immunogenicity. Of 206 patients receiving chemotherapy-containing regimens, 21.4% (44/206) were oxaliplatin-based, 18.5% (38/206) were platinum-doublet, 15% (31/206) were anthracycline-based, 9% (19/206) were treated with paclitaxel, 9% (19/206) with 5-fluorouracil or gemcitabine, 8% (17/206) with irinotecan, 4% (9/206) with docetaxel, and 1.5% (3/206) other chemotherapy agents, namely eribulin, temozolomide and CMF (cyclophosphamide, methotrexate, and fluorouracil) regimens (Figure 3b). Compared to healthy controls, the immune responses were markedly blunted in patients who received anthracycline-based (GMT 5.03 U/mL, 95%CI 1.80–14.09), while significantly diminished in those on paclitaxel (GMT 249.6 U/mL, 95% CI 123.5– 504.5) or oxaliplatin-based regimens (GMT 248 U/mL, 95% CI 120.1–512.7). Of 34 patients who received anthracyclines, 88.2% (30 of 34) and 45.2% (17 of 31) failed to seroconvert at 4-weeks post-first-vaccine (TP2) and 4-weeks post-second-vaccine (TP4), respectively. In contrast, the GMT levels of patients who received 5-fluorouracil or gemcitabine or docetaxel were higher than the other cytotoxic agents.

To assess the magnitude of immune response suppression by different types of cancer treatment, we calculated unadjusted GMR versus healthy controls, and GMR adjusted for the known confounders, age and sex[13] (Figure 3c). The crude and adjusted GMR were similar across all treatments. Eight treatment groups demonstrated significantly poorer immune responses. Anthracycline-based regimens had the lowest GMR of 0.004 (95%CI 0.002– 0.008), in addition to immunotherapy (GMR 0.203, 95%CI 0.109–0.381), paclitaxel (GMR 0.268, 95%CI 0.123–0.581), oxaliplatin-based regimens (GMR 0.340, 95%CI 0.194–0.594), TKI (GMR 0.460, 95%CI 0.294–0.718), irinotecan (GMR

Cancer Cohort (*n*=385)					
Age, median (IQR)	**60**	**(50-68)**	**Cancer types**		
Sex			Breast	116	(30.1%)
Female	239	(62.1%)	Lung	98	(25.5%)
Male	146	(37.9%)	Colorectum	73	(19.0%)
Study site			GIST	18	(4.7%)
CU	230	(59.7%)	Head Neck	17	(4.4%)
PPK	155	(40.3%)	GU	14	(3.6%)
Initial TNM Staging			HCC	13	(3.4%)
I	16	(4.2%)	Esophagus Stomach	11	(2.9%)
II	58	(15.1%)	Biliary Pancreas	8	(2.1%)
III	141	(36.6%)	Skin	7	(1.8%)
IV	170	(44.2%)	Sarcoma	6	(1.6%)
Current disease status			Other	4	(1.0%)
Early	64	(16.6%)	**Cancer treatment**		
Locally advanced	67	(17.4%)	Chemotherapy (CMT)-containing	206	(53.5%)
Recurrence	86	(22.3%)	CMT	168	(43.6%)
De novo metastasis	168	(43.6%)	CMT with Biologics or TKI or IO	38	(9.9%)
Treatment intention			TKI	92	(23.9%)
Adjuvant	97	(25.2%)	Immunotherapy(IO)-containing	35	(9.1%)
Neoadjuvant	27	(7.0%)	IO alone	28	(7.3%)
Palliative	261	(67.8%)	IO with Biologics or TKI	7	(1.8%)
Co-morbidity			CDKi	18	(4.7%)
No	204	(53.0%)	Endocrine therapy	14	(3.6%)
Hypertension	106	(27.5%)	Anti-HER2	13	(3.4%)
Diabetes	57	(14.8%)	PARPi	3	(0.8%)
Dyslipidemia	57	(14.8%)	ADC	2	(0.5%)
Cerebrovascular disease	4	(1.0%)	PI3Ki	1	(0.3%)
COPD	4	(1.0%)	Other	1	(0.3%)
Coronary aterial disease	2	(0.5%)	Radiation	30	(7.8%)
Cirrhosis	9	(2.3%)	**Corticosteroid**		
Autoimmune disease	2	(0.5%)	No	195	(50.6%)
Chronic kidney disease	10	(2.6%)	Pre-medication purpose	183	(47.5%)
Chronic hepatitis B or C	8	(2.1%)	Therapeutic purpose (>10 mg predisolone	7	(1.8%)
Gout	5	(1.3%)	quivalent for more than 7 days)		
Other	61	(15.8%)			

***Table 1*:** Baseline demographics and disease characteristics**.**

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CMT, chemotherapy: TKI, Tyrosine kinase inhibitors; IO, Immunotherapy; PARPi, PARP (poly(ADP)-ribose polymerase) inhibitors; HER2, Human epidermal growth factor receptor 2; CDKi, Cyclin-dependent kinase inhibitor; PI3Ki, Phosphoinositide 3-kinase inhibitor.

0.414, 95%CI 0.183−0.938) and platinum-doublet regimen (GMR 0.520, 95%CI 0.287−0.941). Adjusted GMR in the small heterogenous group of other therapies was also significantly reduced compared to controls (GMR 0.091, 95%CI 0.027−0.310). Treatment with anti-HER2 (GMR 0.903, 95%CI 0.359−2.271) or endocrine therapy (GMR 0.736, 95%CI 0.302−1.792) or 5-fluorouracil or gemcitabine (GMR 0.863, 95%CI 0.397 −1.876) or docetaxel (GMR 0.706, 95%CI 0.238 −2.097) had GMR which were closer to the null ratio of 1, but the lower 95% CI was below a level that would be considered inferior in vaccine licensing studies.[14]

Antibody titers distributions by other baseline characteristics: disease status, treatment aim, sex or age dichotomized at 60 years were similar. Titers by tumor types were shown heterogeneity of response, and are likely confounded by treatment regimen. Additionally, steroid use was associated with reduced antibody levels, and likely due to the use of these agents as antiemetic pre-medications among those receiving cytotoxic chemotherapy regimens (Figure S3).

Neutralization against SAR-CoV-19 wild type and delta strains

A subset of 91 samples at 4-week after the second vaccine (TP4) were evaluated for neutralizing activity against the SAR-CoV-2 wild-type strain and the variant

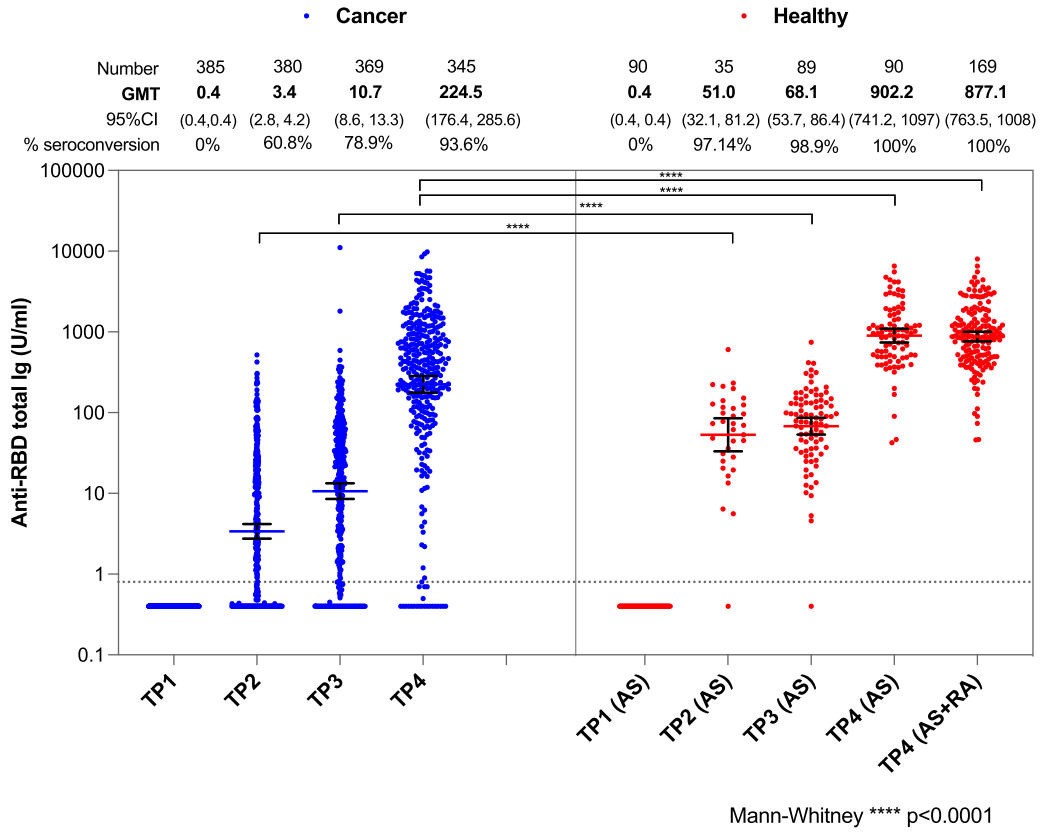

Figure 2. Kinetics of antibody response following two-dose ChAdOx1-nCoV-19 vaccines in cancer patient versus healthy adults.

Geometric mean titres (GMT) with 95% confidence interval (CI) of anti-RBD total Ig levels by study group. The healthy controls were from two cohorts: AS and RA cohorts**.** TP1, Time-point 1: before first dose; TP2, Time-point 2: 4-week post first dose; TP3, Time-point 3: before second dose; TP4, Time-point 4: 4-week post second dose; **** $p<0.0001$

The conversion factor from Roche U/ml to BAU/ml is to divided U/ml with 0.972.

of concern B.1.617.2 (Delta strain) using the surrogate virus neutralization test (sVNT). Cohort characteristics were showed in supplementary Table S6. A good correlation between $\log_{10}$ anti-RBD total-Ig and neutralization (NT) percentage against wild-type or delta strain was observed (Figure 4a). Consistent with anti-RBD total-Ig responses, detectable neutralization against both wild-type and delta strain in cancer patients (wild-type 82.4%, delta 73.62%) was significantly lower than those of healthy controls (wildtype 100%, delta 100%) (Figure 4b). Within the cancer cohort, neutralizing activity against delta strain was significantly reduced compared to the wild-type strain (Wilcoxon sign rank test, $p<0.0001$). The median %sVNT were significantly lower for Delta strain, as compared to wild type, in both cancer patients and healthy cohort. The concordance rates between detectable anti-RBD antibody and positive %sVNT were 90.1% and 83.5% for wild-type and Delta strains, respectively.

Local and systemic adverse reactions after each vaccination

Adverse events following each vaccination were assessed in all 399 patients who received the first vaccination and 359 of 367 patients who received the second vaccination. The incidence of local and systemic adverse events (AEs) was higher after the first dose than the second dose (any AEs 63.7% vs. 50.7%). The severity of side effects from vaccination was mostly mild or moderate and no serious adverse events reported. Pain was the most commonly reported local reaction found in 157/399 (39.3%) participants after the first dose and 108/359 (30.1%) after the second dose. Fatigue was the most commonly reported systemic reaction, reported in 38.8% (153/399) and 27.3% (98/359) participants after the first and second doses, respectively. Other common systemic adverse reactions were myalgia and headache. Myalgia was reported by 33.6% (134/399) and 23.7% (85/359), whereas headaches were 29.3% (117/399) and

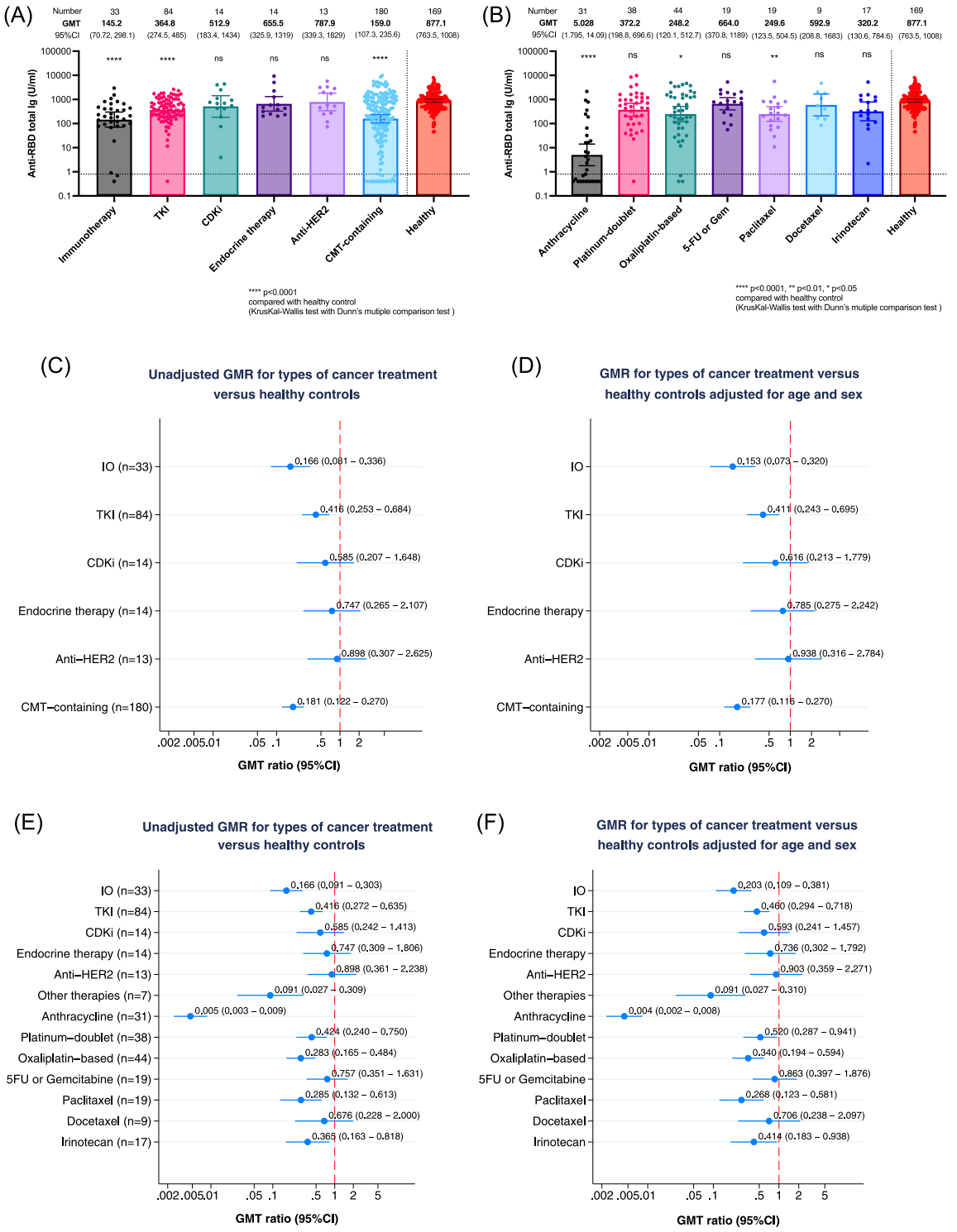

Figure 3. Antibody responses 4-weeks following the second dose of ChAdOx1-nCoV-19 vaccine by types of cancer treatment versus healthy controls.

(A) Anti-RBD total Ig GMT levels (95%CI) by types of cancer treatment.

(B) Anti-RBD total Ig GMT levels (95%CI) by subgroups of different cytotoxic chemotherapy regimens

(C) The unadjusted and adjusted GMT ratios (GMR) for types of cancer treatment versus healthy controls. Left panel shows unadjusted GMR, and right panel GMR are adjusted for age and sex.

17% (61/359) participants after the first and second vaccinations, respectively. (Figure S4 and Table S3)

Discussion

Our study found the delayed and lower immunogenicity following vaccination with the ChAdOx1-nCoV-19 vaccine in solid cancer patients undergoing active cancer treatment. Seroconversion rates were 60.8% (95%CI 55.7–65.7) and 78.9% (95%CI 74.-82.9) at 4-weeks, and 8–10-weeks after the first dose, and 93.6% (95%CI 90.5–96) seroconversion at 4-weeks after the second dose. The rates in our comparator heathy controls were 97.1% (95%CI 84.7–99.9), 98.9% (95%CI 93.9–100), and 100% (95%CI 97.8–100) at the same timepoints. The age and sex adjusted GMT of anti-RBD total Ig were 4-fold lower after the complete two-dose vaccination (GMR 0.25, 95%CI 0.168–0.366). These findings are consistent with those reported in solid tumour patients following vaccination with mRNA vaccines,[7,15-17] or cohorts of solid tumour patients where mRNA and adenoviral vector vaccinated patients have been combined.[18,19]

This study demonstrated lower immunogenicity to ChAdOx1-nCoV-19 vaccine in solid cancer patients undergoing active cancer treatment. In cancer patients, all reports of COVID vaccine efficacy were in patients receiving mRNA vaccines. Only few studies included patients receiving adenoviral vector vaccines. Among those, the CAPTURE study was only one study with the majority receiving adenoviral vector vaccine.[18] Unlike the current study measuring anti-RBD total I_g, CAPTURE study primarily used live virus neutralization assay. Although, both studies demonstrated lower immunogenicity, but seroconversion rate and detectable neutralized antibody to Delta variant were lower in CAPTURE study. While different treatment type was significantly associated with different immune response in this study, but not in CAPTURE study. These different findings might be related to differences in study population, immunogenicity assessment and statistical analysis.

While previous studies have shown chemotherapeutic agents could attenuate immune response after vaccination, most of these studies have compared a heterogenous mix of chemotherapy regimens as a single group, to immune responses observed in healthy controls.[6,16,20,21] Our study showed the attenuation in immune responses to COVID-19 vaccination differed by chemotherapy regimens. Types of systemic therapy and regimens of cytotoxic agents impacted differently on the immunogenicity against SARS-CoV-2. It was obviously attenuated in patients receiving cytotoxic agents and immunotherapy. Interestingly, for cytotoxic agents, vaccination in patients receiving anthracycline-based regimens (doxorubicin/epirubicin and cyclophosphamide/ ifosfamide) failed to induce adequate antibody responses: seroconversion rates were 55% at 4 weeks following the complete vaccination schedule and the adjusted GMR was 0.0044 (95%CI 0.003–0.009), much lower than other cytotoxic agents/ regimens. Among 15 seronegative patients, majority of patients were age less than 60 years, with early-stage cancer and without significant comorbidity, as shown in Table S4. Therefore, this particular regimen might be more potent in attenuation of immunogenicity to ChAdOx1-nCoV-19 vaccine in cancer patients, as compared to other agents. However, these results should be confirmed by larger studies.

Among non-cytotoxic systemic treatments, patients who received immunotherapy, mostly immune-checkpoints inhibitors also had markedly attenuated immunogenicity with seroconversion rates of 45.7%, and 37.5% 4-weeks, and 8–10-weeks after the first dose and 93.9% 4 weeks after the complete vaccination course, with GMR of 0.203 (95%CI 0.109–0.381) versus controls. The results were in line with a prospective study in Greece reporting low titers and 25% seroconversion of cPass SAR-CoV-2 neutralizing antibody at 3-week after the first vaccine (75% mRNA vaccine, 25% ChAdOx1-nCoV-19) in 59 patients with solid cancer receiving immune check-point inhibitors.[22] In contrast, the VOICE trial in the Netherlands did not find the impact of immunotherapy on the humoral immune response to mRNA1273 vaccine with 99.2% seroconversion at 4-weeks after the second dose.[8] However, among these studies, there were significant differences, including cancer types, types vaccine, and interval of immunotherapy administration before vaccination, likely contributing to the different immunogenicity findings.

No new vaccine-related safety signals were observed in our study. Local and systemic adverse events reported by cancer patients were mostly mild or moderate and were less frequent in number after the second vaccination. Consistent with the reduced immunogenicity versus the previously published healthy individuals,[23-25] the local and systemic adverse event rates in solid tumor patients was also lower compared to the healthy adults. This is most likely because these reactions are at least partially mediated by an immune mechanism.

Our study has a number of limitations. Observational studies are subject to confounding. Age is known

(D) The unadjusted and adjusted GMT ratios (GMR) for types of cancer treatment versus healthy controls. Left panel shows unadjusted GMR, and right panel GMR are adjusted for age and sex. Cytotoxic chemotherapy regimens have been separated by drug classes in the lower part of each panel.

IO, immunotherapy; TKI, tyrosine kinase inhibitors; CDKi, Cyclin-dependent kinase inhibitor; HER2, Human epidermal growth factor receptor 2; CMT, chemotherapy; 5FU, 5-fluorouracil; Gem, gemcitabine; ns, not significant; **** $p<0.0001$, ** $p<0.01$, * $p<0.05$.

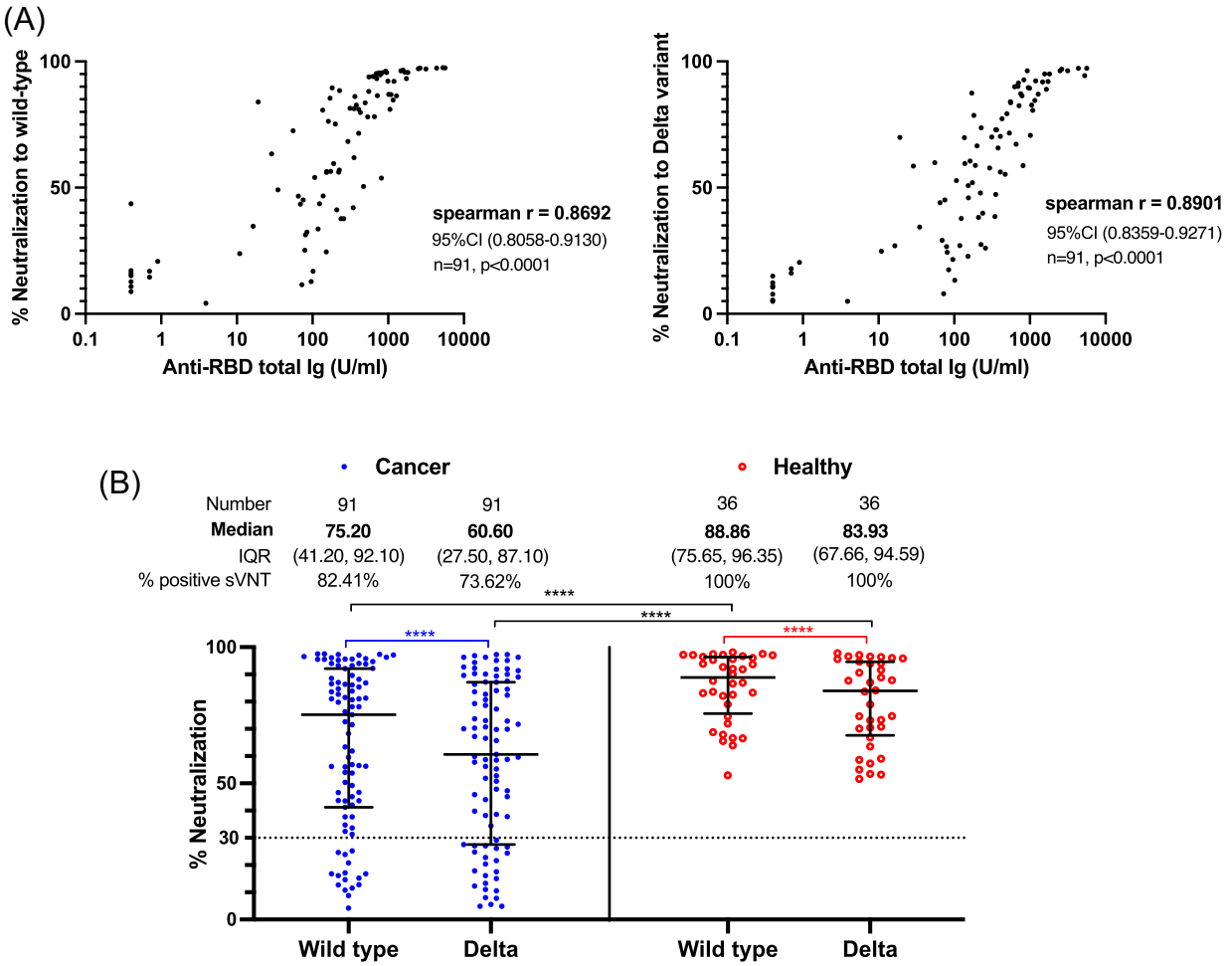

Figure 4. Neutralization against SARS-CoV-2 wild-type and Delta strain. (A) Correlation between anti-RBD total Ig and surrogate virus neutralization test (sVNT) Neutralization against wild-type or delta strain. (B) Surrogate virus neutralization test (sVNT) at 4-week after the complete 2-dose vaccination in subset of 91 patients with cancer versus heathy controls (*n*=36). The percentage of neutralization was reported as median +/- IQR. Inhibition of ≥30% was considered positive. **** $p<0.0001$.

to influence immune responses and the mean age of our healthy controls was substantially younger than our oncology cohort. To mitigate this limitation, we adjusted our GMT for age and sex. However, we could not run the adjusted analysis for other potential confounding factors, such as comorbidity, steroid use or BMI, due to the lack of data in the healthy control. The GMT levels for each subgroup according to those factors were in line with main results, shown in Figure S3. Thus, it is possible that comorbidities, or other unmeasured confounders may have influenced our results. In addition, age-matched ad-hoc analysis gave the same findings to the main result.

Apart from the anticancer treatment given, numerous factors including intrinsic host factors and extrinsic factors could potentially influence vaccine immunogenicity. Second, some of our chemotherapy and systemic treatment subgroups were small. Nevertheless, the 95%CI around our GMR quantitate the degree of uncertainty in our estimates would provide physicians with some information regarding expected vaccine responses according to treatment regimen. Larger participant numbers in each drug class from pooled analyses could confirm, and estimate these findings with greater precision. Third, this study used anti-RBD total Ig, but not live virus neutralization, to assess immunogenicity. However, our surrogate neutralization in a subgroup of 91 patients confirmed the lower immunogenicity in cancer patients compared to healthy and neutralization against delta strain is significantly lower than wild-type strain in cancer and healthy cohort, similar to previous reports.[26,27]

Despite these limitations, our study results provide oncologists with some evidence regarding the impact of different systemic therapies, on the likely immunogenicity of ChAdOx1-nCoV-19 vaccination, even though precise mechanisms of reduced immunogenicity induced by each regimen remain unknown.

In summary, cancer patients receiving systemic treatment especially chemotherapy and immunotherapy had reduced vaccine immunogenicity. Caution about inadequate immunity and higher risk for COVID-19 infection could be raised. Despite no established correlation of protection, antibody measurement could be implemented in these groups of oncologic patients at high risk for low immunogenicity. Additional COVID-19 vaccine should be offered to reach the optimal protection in those with poor humoral immune responses. Nevertheless, patients receiving different chemotherapy regimens could have different response to COVID-19 vaccinations. Further research focusing on these contributing factors and the pooled analyses that allows expanding sample size is anticipated to refine the strategic management about COVID-19 vaccination in solid cancer patients undergoing active treatment.

Contributors

Conceptualization and study design: SL, NT, PW, PS, NP, NW, EP, SK
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Recruited patients: NT, SL, NP, PS, NP, PS, NP, CV, ST, VS, PW, TK, PI, TN
Clinical database: SL, NT, PW, PS, NP
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Data sharing statement

Data are available upon reasonable request to the corresponding author after an approval of proposal and a signed data access agreement.

Declaration of interests

SK received grants from US National Institutes of Health and Foundation for AIDS Research. Other declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101608.

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