Vaccine-Related adverse events following AZD1222 (ChAdOx1-nCoV-19) Covid-19 vaccine in solid malignancy patients receiving cancer treatment, as compared to age-matched healthy controls

Nussara Pakvisal1, Panot Sainamthip2, Nattaya Teeyapun3, Sutima Luangdilok4, Wassamon Wanlapakorn5, Rithidech Yorsaeng6, Yong Poovorawan6, Piypoom Pakvisal7, Thiti Susiriwatananont8, Nicha Zungsontiporn5, Virote Sriuranpong2, Suebpong Tanasanvimon3, and Passakorn Wanchajiraboon7

*Division of Medical Oncology, Department of Medicine, Chulalongkorn University and the King Chulalongkorn Memorial Hospital, Bangkok, Thailand; 1Department of Pharmacology, Chulalongkorn University and the King Chulalongkorn Memorial Hospital, Bangkok, Thailand; 2Department of Biochemistry, Chulalongkorn University and the King Chulalongkorn Memorial Hospital, Bangkok, Thailand; 3Center of Excellence in Clinical Virology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University and the King Chulalongkorn Memorial Hospital, Bangkok, Thailand; 4Department of Medicine, Police General Hospital, Bangkok, Thailand; 5Phrapokklao Cancer Center of Excellence, Phrapokklao Clinical Research center, Phrapokklao Genomic Laboratories, Phrapokklao Hospital, Chantaburi, Thailand

ABSTRACT
The study aimed to evaluate vaccine-related adverse events (VRAEs) following ChAdOx1-nCoV-19 vaccine in solid cancer patients receiving treatment compared to healthy controls. 399 cancer patients and 90 healthy volunteers were enrolled. In the overall population, the incidence of VRAEs was significantly lower in cancer patients than in healthy volunteers (57% vs 80%, P < .001). Because the mean age of the cancer patients was higher than the healthy volunteers (59 vs 48 years, P < .001), we analyzed age-matched comparison and found that there was no significant difference of VRAEs between two groups (74% vs 79%, P = .32). Most VRAEs were of mild severity in both groups. The most common local VRAE was pain at the injection site in both groups, and the most common systemic VRAE was fatigue in the cancer cohort, whereas myalgia was the most common VRAE among the healthy controls. In the cancer cohort, fever was the only VRAE that led to interruption of the cancer treatment (in two cases). Among the cancer treatment types, patients undergoing chemotherapy-containing regimens had a lower likelihood of experiencing VRAEs. In summary, the overall incidence of VRAEs following ChAdOx1-nCoV-19 vaccine in actively treated cancer patients was comparable to healthy controls after adjusting for age. The VRAEs that occurred rarely interfered with the cancer treatment. These findings substantiate that vaccination with AZD1222 is safe in cancer patients undergoing treatment.

Introduction
The Covid-19 pandemic has led to a number of consequences for cancer care, including a delay in cancer diagnosis and treatment. Moreover, several studies have found that cancer patients infected with COVID-19 face a higher risk of serious complications and death than the general population.1–3 One possible reason is that the cancer patients might be immunocompromised by the effect of antineoplastic therapy, supportive medications such as steroids, and the immunosuppressive properties of cancer itself.2,4 Many different types of Covid-19 vaccine have been developed and proven to reduce the risk of SARS-CoV-2 infection and the likelihood of developing a serious illness. Unfortunately, data on safety in malignancy patients, particularly those receiving cancer treatment, is lacking because they are excluded from vaccine trials.4–8 Currently, the safety data regarding Covid-19 vaccines in actively treated cancer patients is limited to a few studies that have focused on messenger RNA (mRNA) vaccines, including BNT162b2 and mRNA-1273.10 However, studies on the viral-vector vaccine, ChAdOx1-nCoV-19, are scarce. The mRNA-based vaccine is a relatively new technology that employs molecular templates of messenger RNA to deliver the genetic information to produce the spike glycoprotein antigen, not to deliver the antigen itself,11 whereas the viral vector-based vaccine uses a non-replicating harmless version of adenovirus as a vehicle to deliver the spike glycoprotein antigen’s genetic code, eliciting the targeted immune response.12 Because two types of vaccines have differences in their mechanisms of action, the adverse effects experienced by cancer patients might also differ.

In Thailand, most cancer patients were immunized with the ChAdOx1-nCoV-19 vaccine during the early phase of the vaccination program, prioritizing vulnerable groups, in June 2021. However, vaccine hesitancy is one of the issues of concern among malignancy patients.10–13,14–17 Such hesitation is generally due to a fear of side effects, especially among those undergoing cancer treatment.14,16,17

CONTACT Passakorn Wanchajiraboon passakorn@gmail.com Phrapokklao Cancer Center of Excellence, Phrapokklao Clinical Research center, Phrapokklao Genomic Laboratories, Phrapokklao Hospital, Mueang District, Chantaburi 22000, Thailand

*Co-first author
Supplemental data for this article can be accessed on the publisher’s website at https://doi.org/10.1080/21645515.2022.2094149

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As a result, we aimed to evaluate vaccine-related adverse events (VRAEs) in actively treated solid malignancy patients following one and two doses of ChAdOx1-nCoV-19 vaccine compared to healthy controls. Previous literatures reported younger age as being associated with greater risk of developing VRAEs, so we analyzed an age-matched comparison to reduce this bias. In addition, we conducted an exploratory analysis to identify individual risk factors related to reactogenicity in the cancer cohort.

**Material and methods**

**Study population**

This was a multicenter prospective cohort study conducted at King Chulalongkorn Memorial Hospital (CU) and Phrapokklao Hospital (PPK). We enrolled solid cancer patients who were actively receiving cancer treatments between June 18 and 27 July 2021. Patients with a history of SARS-CoV-2 infection or life expectancy of less than 6 months were excluded from the study. Patient demographics, disease characteristics, and data related to cancer treatments were reviewed and recorded at study entry and at each visit. We employed the Eastern Cooperative Oncology Group Performance Status (ECOG PS) score with six points, ranging from 0 (fully active) to 5 (dead) in assessing patient physical condition (Table S1 in supplementary material). The patients received two doses of ChAdOx1-nCoV-19 vaccine, administered at an interval of 8 to 10 weeks.

After each dose of vaccine, the patients were asked to self-report adverse events that did not include the previous symptoms from their cancers or cancer treatments using paper-based or electronic online questionnaires (supplementary material) for at least 7 consecutive days from the day of injection. Solicited adverse events in the questionnaire were classified into two categories. The first was local adverse effects, including pain, swelling, and erythema at the injection site. The second comprised systemic adverse effects, including fever, headache, myalgia, fatigue, nausea or vomiting, arthralgia, diarrhea, back pain, dizziness, and lymphadenopathy, which is described as the palpation of a lump or mass in the axilla or neck area. Physical examination by a physician at an oncology clinic and review of all imaging performed after each dose of vaccination were also used to determine the incidence of lymphadenopathy. Unsolicited adverse events were reported by patients themselves.

Four weeks after receiving each dose of ChAdOx1-nCoV-19 vaccine, all participants were required to visit an oncology clinic for a face-to-face consultation to obtain a medical history, have a physical examination and clarify with the investigator who was a medical oncologist, that reported adverse events were related to the vaccine or not. In our study, vaccine related adverse event (VRAE) was defined as a medical event that occurred following the vaccination and believed to be caused by the vaccine based on the patient’s and investigator’s judgments. Because all patients in our study were receiving cancer treatment during vaccination, we used baseline patients’ symptoms, the common side effects of their individual cancer therapy and temporal relationship to verify all reported adverse events. We also gathered adverse events of interest, including vaccine-induced immune thrombotic thrombocytopenia and thrombosis, by reviewing all laboratory data and medical records. The severity of vaccine related adverse events (VRAEs) was graded by the investigator according to the FDA’s toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials to four grades as following: grade 1, mild symptom and not interfere with activity; grade 2, moderate symptom and some interferes with activity but not requiring medical intervention; grade 3, severe symptom and prevents daily activity or requires medical intervention; grade 4, life threatening symptom and needs emergency room visit or hospitalization. The details of each grade in each adverse event were described in the questionnaire (supplementary material). Blood samples were taken from all patients to test their immunogenicity before the first dose, 4 weeks after the first dose, and then again 4 weeks after the second dose (Figure 1). 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 the Elecsys SARS-CoV-2 S assay according to the manufacturer’s instructions (Roche Diagnostics, Basel, Switzerland). The detection limit of the assay is 0.4 U/mL, while antibody values of 0.8 U/mL indicates positive seroconversion. The result of the immunogenicity testing was reported in an earlier study. In this study, we also collected the incidence of COVID-19 infection, which was detected using an antigen test kit or a nasopharyngeal polymerase chain reaction (PCR) after each dose of vaccine.

The study was done in conformity with the principles of the Declaration of Helsinki, with all patients providing written informed permission, and 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).

**Figure 1.** Consort diagram of cancer cohort.
Healthy individuals

Ninety healthy volunteers who received two doses of the ChAdOx1-nCoV-19 vaccine with a 10-week interval at King Chulalongkorn Memorial Hospital between March and May 2021 were used as a comparison group. Solicited and unsolicited VRAEs were collected using questionnaires for at least 7 consecutive days. There were 3 and 1 missing data in adverse events after the first and second dose, respectively. As a result, there were 87 and 89 healthy volunteers following the first and second vaccinations, respectively, in the analysis.

Outcomes

The primary endpoint was incidence and severity of VRAEs among actively treated solid cancer patients, as compared to healthy controls in an overall population and age matched group. The secondary end points were assessment of onset and duration of VRAEs, incidence of VRAEs interrupted cancer treatment, seroconversion rate and incidence of Covid-19 infection in cancer patients. We also undertook exploratory analysis to evaluate individual risk factors associated with vaccine reactivity after the first and second vaccinations in the cancer cohort.

Statistical analysis

Descriptive statistics were used for demographics, disease characteristics, and data on cancer treatments. The difference in incidence and severity of VRAEs between the cancer and healthy cohorts was analyzed by the chi-square test. We also used age-matched one-to-one comparison to analyze the difference between the two groups. For measuring association among individual risk factors and the risk of developing VRAEs, we applied a univariate logistic regression analysis to calculate an unadjusted hazard ratio. The significant factors from the univariate analysis were included in the multivariate analysis to determine the independent factors. P-values of less than 0.05 were considered statistically significant.

We used SPSS version 28.0 (IBM Corp., Armonk, NY) and Stata 15 (Statacorp LLC, College Station, TX) for statistical analyses. Two-sided p values level <.05 were considered statistically significant.

Results

Patient characteristics

Between June 18 and 27 July 2021, 399 solid malignancy patients on active cancer treatment were recruited for the study and received the first dose of the ChAdOx1-nCoV-19 vaccine. Of these, 369/399 (92.5%) received the second dose of the ChAdOx1-nCoV-19 vaccine and were included in the analysis. 7.5% of patients (30 of 399) did not receive the second dose at 8–10 weeks later due to either cancer-related deaths (n = 7), SARS-CoV infections (n = 11) or study withdrawal (n = 12) (Figure 1).

The mean age of solid cancer patients was 59 years (range 16–96 years) and 62% were female. At enrollment, most patients had metastasis disease (n = 268, 67.2%). All patients were receiving systemic cancer treatment during the first vaccination (Table 1). 359 of 369 (97.3%) patients who received the second vaccination continued anti-cancer treatments. Concurrent steroid use during vaccination was 45.9% (183/399) and 34.7% (128/369) after the first and second dose, respectively. The most common reason for steroid use was for pre-medication purpose (97.3%). The seroconversion rate was 58.4% and 87.3% at 4 weeks after the first and second doses of the ChAdOx1-nCoV-19 vaccine, respectively.

For the 90 healthy volunteers who received the ChAdOx1-nCoV-19 vaccine, the mean age was 43 years (range 19–85 years) and 55% were female. In the healthy cohort, the

Table 1. Patient demographics and disease characteristics in cancer cohort.

| Characteristics                              | All cancer patients N = 399 (%) |
|----------------------------------------------|---------------------------------|
| Age, median (IQR)                            | 61 (51–69)                      |
| Female, n (%)                                | 247 (61.9%)                     |
| ECOG PS, n (%)                               |                                |
| 0                                            | 67 (16.8%)                      |
| 1                                            | 311 (77.9%)                     |
| 2                                            | 21 (5.3%)                       |
| BMI Mean, (range)                            | 22.7 (13.7–37.2)                |
| BMI group, n (%)                             |                                |
| <18.5 (underweight)                          | 57 (14.3%)                      |
| 18.5–24.9 (normal)                           | 346 (89.1%)                     |
| ≥25 (overweight)                             | 106 (26.6%)                     |
| Comorbidity                                  |                                |
| No                                           | 214 (53.6%)                     |
| Hypertension                                 | 109 (27.3%)                     |
| Diabetes                                     | 60 (15.3%)                      |
| Dyslipidemia                                 | 59 (14.8%)                      |
| Chronic liver disease                        | 16 (4%)                         |
| Chronic kidney disease                       | 12 (3%)                         |
| Chronic obstructive pulmonary disease        | 9 (2.3%)                        |
| Coronary heart disease                       | 9 (2.3%)                        |
| Cerebrovascular disease                      | 6 (1.5%)                        |
| Gout                                         | 5 (1.3%)                        |
| Autoimmune disease                           | 5 (1.3%)                        |
| Current disease status, n (%)                |                                |
| Early                                        | 46 (11.5%)                      |
| Locally advanced                             | 85 (21.3%)                      |
| Metastasis                                   | 268 (67.2%)                     |
| Cancer type, n (%)                           |                                |
| Breast                                       | 119 (29.8%)                     |
| Lung                                         | 99 (24.8%)                      |
| Colorectal                                   | 76 (19%)                        |
| Hepatocellular carcinoma                     | 13 (3.3%)                       |
| Pancreaticobiliary                           | 10 (2.5%)                       |
| Esophagogastric                              | 12 (3%)                         |
| Gastrointestinal stromal tumor               | 19 (4.8%)                       |
| Head neck                                    | 18 (4.5%)                       |
| Genitourinary                                | 16 (4%)                         |
| Melanoma and skin                            | 7 (1.8%)                        |
| Sarcoma                                      | 6 (1.5%)                        |
| Other                                        | 4 (1%)                          |
| Cancer treatment, n (%)                      |                                |
| Chemotherapy                                 | 206 (51.6%)                     |
| Targeted therapy/Biologic agents             | 138 (34.6%)                     |
| Immunotherapy                                | 38 (9.5%)                       |
| Hormonal therapy                             | 15 (3.8%)                       |
| Combination chemotherapy and immunotherapy  | 2 (0.5%)                        |
| Radiation                                    | 36 (9%)                         |
| Corticosteroid use, n (%)                    |                                |
| No                                           | 216 (54.1%)                     |
| Pre-medication purpose                      | 178 (44.6%)                     |
| Therapeutic purposes                         | 5 (1.3%)                        |
| Influenza vaccine, n (%)                     | 21 (5.3%)                       |

IQR, Interquartile range; ECOG, Eastern Cooperative Oncology Group; PS, performance status; BMI, Body mass index.
Seroconversion rates were 96.7% and 98.9% following the first and second dose of the ChAdOx1-nCoV-19 vaccine, respectively.

**Vaccine related adverse events**

**Cancer cohort**

Vaccine-related adverse events (VRAEs) were assessed in 399 cancer patients after the first vaccination and in 369 cancer patients after the second dose. The incidence of any VRAE was higher following the first dose than the second dose (63.2% vs 51.2%, \( P = 0.04 \)). The severity of VRAEs was mostly mild or moderate, and no serious adverse events were reported. Pain at the injection site (first dose 39%, second dose 30%) and fatigue (first dose 38%, second dose 27%) were the most common of any grade of local and systemic VRAEs, respectively. The most common grade 3 VRAEs were fatigue (1%) after the first dose and pain at the injection site (2%) after the second dose (Figure 2). The incidence of VRAEs among cancer treatment types following the first and second vaccinations is shown in Tables 2 and 3. The median onset of any VRAE was 1 day (range 0–8 days), and the median duration was 2 days (range 1–18 days) after the first or second vaccination. The incidence of each VRAE on each day for seven days is shown in Figure 3. Fever was the only VRAE that led to interruption of the cancer treatment (in two cases; 0.5%). In both cases chemotherapy was
Table 2. Incidence of vaccine-related adverse events among cancer treatment types after first vaccination.

| VRAE       | All N = 399 (%) | Targeted/ Endocrine therapy N = 153 (%) | CMT N = 206 (%) | IO N = 38 (%) | CMT + IO N = 2 (%) | P-value |
|------------|-----------------|----------------------------------------|-----------------|--------------|--------------------|---------|
| Any        | 252 (63.2)      | 121 (79.1)                             | 98 (47.6)       | 32 (84.2)    | 1 (50)             | <.001   |
| VRAEs Local|                 |                                        |                 |              |                    |         |
| Pain       | 156 (39.1)      | 75 (49)                                | 59 (28.6)       | 21 (55.3)    | 1 (50)             | <.001   |
| Swelling   | 32 (8)          | 17 (11.1)                              | 10 (4.9)        | 5 (13.2)     | 0                  | .09     |
| Erythema   | 15 (3.8)        | 8 (5.2)                                | 7 (3.4)         | 0            | 0                  | .47     |
| Systemic   |                 |                                        |                 |              |                    |         |
| Fever      | 33 (8.3)        | 14 (9.2)                               | 15 (7.3)        | 4 (10.5)     | 0                  | .84     |
| Headache   | 117 (29.3)      | 56 (36.6)                              | 46 (22.3)       | 15 (39.5)    | 0                  | .01     |
| Myalgia    | 133 (33.3)      | 70 (45.8)                              | 48 (23.3)       | 15 (39.5)    | 0                  | <.001   |
| Fatigue    | 152 (38.1)      | 73 (47.7)                              | 60 (29.1)       | 19 (50)      | 0                  | <.001   |
| Nausea/    | 52 (13)         | 23 (15)                                | 26 (12.6)       | 3 (7.9)      | 0                  | .63     |
| Vomiting   |                 |                                        |                 |              |                    |         |
| Diarrhea   | 67 (16.8)       | 37 (24.2)                              | 26 (12.6)       | 10 (25.9)    | 0                  | .02     |
| Arthralgia | 30 (7.5)        | 13 (8.5)                               | 13 (6.3)        | 4 (10.5)     | 0                  | .73     |
| Back pain  | 34 (8.5)        | 18 (11.8)                              | 10 (6.3)        | 6 (15.8)     | 0                  | .04     |
| Dizziness  | 46 (11.5)       | 24 (15.7)                              | 15 (7.3)        | 7 (18.4)     | 0                  | .04     |

VRAE, vaccine-related adverse event; CMT, chemotherapy; IO, immunotherapy.

 postponed for 3 days when the patients developed grade 2 fevers (one case after the first dose and one case after the second dose). None of the patients who had VRAEs required hospitalization. Of interest, two patients experienced worsening of preexisting treatment-related grade 2 rash after the first and second vaccinations (one receiving an immune checkpoint inhibitor, Pembrolizumab, and 1 receiving an EGFR tyrosine kinase inhibitor, Erlotinib) and one patient receiving Pertuzumab and Trastuzumab developed grade 2 polyarthritis and required steroid treatment after the second dose of vaccine. There was no incidence of vaccine-induced immune thrombotic thrombocytopenia, thrombosis, or lymphadenopathy in our cohort.

At the time of data cut off (31 January 2022), 17 of 399 cancer patients (4.3%) had been diagnosed with Covid-19 infection. Covid-19 infection was detected in 11 patients (64.7%) and 6 patients (35.3%) following the first and second vaccinations, respectively. Median time from day of vaccination to diagnosis of Covid-19 infection was 53 days and 24 days after the first and second doses, respectively. All infected patients received antiviral treatment, and 14 of 17 patients (82.3%) required hospitalization. Only two of the 17 patients (11.8%) required oxygen support, but no one required ventilator support. No deaths from Covid-19 infection were reported in our cohort.

Exploratory analysis was performed to identify individual risk factors associated with vaccine reactogenicity. We found that age, performance status, staging and cancer treatment were the independent risk factors following the first dose of ChAdOx1-nCoV-19 vaccine. Non-elderly (age <65), poor performance status (ECOG 2), and metastasis-stage patients had a higher risk of VRAEs, while patients receiving a chemotherapy-containing regimen or radiation had a lower risk (Table 4). For the second dose of ChAdOx1-nCoV-19 vaccine, the independent risk factors were experiencing VRAEs after the first dose, and duration between the first and second vaccination. Patients who experienced VRAEs following the first dose had a greater risk of developing VRAEs, while patients who got the second dose 10 weeks after the first dose had a decreased risk (Table 5).

Healthy cohort

Vaccine-related adverse events were analyzed in 87 and 89 healthy volunteers following the first and second vaccinations, respectively. The incidence of any VRAE was higher after the first dose than the second dose (93% vs 66%, P = .02). Pain at the injection site and myalgia were the most common of any grade of local and systemic VRAEs, respectively (Figure 2).

Cancer vs healthy cohort

In the overall population, the incidence of any VRAE was significantly lower in cancer patients than in healthy controls (57% vs 80%, P < .001 in overall periods, 63% vs 93%, P < .001 after first dose; and 51% vs 66%, P = .01 after second dose). The incidence, severity and difference of each VRAE between cancer patients and healthy controls following the first and second vaccination are shown in Figures 2 and 4. However, the mean age of cancer patients was significantly higher than healthy volunteers (59 ± 13 vs 48 ± 13 years, P < .001). Therefore, we performed an age-matched comparison including 76 cancer
patients and 75 healthy volunteers. In age-matched analysis, the incidence of VRAEs in cancer patients was significantly lower than that of the healthy controls after the first dose (82% vs 93%, \( P = .03 \)), but not after the second dose (64% vs 67%, \( P = .77 \)) or when evaluating the overall period (74% vs 79%, \( P = .32 \)). There was no significant difference in severity of VRAEs between two groups following the first and second doses. Nevertheless, cancer patients experienced more fatigue, nausea/vomiting, and back pain, while healthy volunteers experienced more pain and erythema at the injection site after both doses of vaccine (Table 6 and Figure 4).

**Discussion**

The study results support the safety of the ChAdOx1-nCoV-19 vaccine in actively treated solid malignancy patients. In the overall population, the incidence of VRAE in cancer patients was significantly lower than in healthy volunteers. When we compared the demographic data between two groups, we found no statistical difference in the proportion of female sex (62% in the cancer cohort and 55% in the healthy cohort, \( P = .19 \)), but the cancer patients were significantly older than the healthy volunteers. To reduce the bias from age difference, we analyzed age-matched comparison and the final result showed the incidence of any VRAE in cancer patients was comparable to healthy controls. However, cancer patients experienced more fatigue, nausea/vomiting, and back pain, while healthy volunteers experienced more local reactions including pain and erythema at the injection site after both doses of vaccination. This may be due to some systemic VRAEs overlapping with the side effects of cancer therapy and the symptoms of cancer.

Interestingly, we found the incidence and severity of local and systemic VRAEs following the first dose was higher than the second dose of ChAdOx1-nCoV-19 vaccine in the cancer cohort, which is similar to the previous results of viral-vectorized vaccine studies in healthy population\(^{25,26} \) and HIV infected patients\(^{27,28} \) but different from the previous result of an mRNA vaccine study.\(^{10} \) When comparing the pattern of VRAEs in cancer patients undergoing treatment across the ChAdOx1-nCoV-19 vaccine in our study (N = 399), the BNT162b2 vaccine in Israel study (N = 218), and the mRNA-1273 vaccine in the Netherlands study (N = 503), we found that the BNT162b2 vaccine resulted in more local reactions\(^{9} \) and mRNA-1273 vaccine produced more systemic reactions\(^{10} \) than the ChAdOx1-nCoV-19 vaccine. We postulate that the difference in reactogenicity between mRNA and adenoviral vector vaccine might probably be caused by the different immune response mechanisms.\(^{24,29} \) The peak T cell response of the adenoviral vector vaccine occurs after the first dose, while that of the mRNA vaccine occurs after the second dose.\(^{30-33} \)

Despite this, prevalence and severity of solicited VRAEs were similar among the three vaccines. All three studies showed that pain at the injection site was the most common local VRAE, while fatigue was the most common systemic VRAE.\(^{9,10} \) The severity of VRAEs was mostly mild or moderate grade, and no

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**Table 3. Incidence of vaccine-related adverse events among cancer treatment types after second vaccination.**

| VRAE       | All N = 369 (%) | Targeted/Endocrine therapy N = 139 (%) | CMT N = 185 (%) | IO N = 34 (%) | CMT+IO N = 1 (%) | No treatment N = 10 (%) | \( P \)-value |
|------------|----------------|---------------------------------------|----------------|--------------|-----------------|-------------------------|-------------|
| Any VRAEs  | 189 (51.2)     | 91 (65.5)                              | 76 (41.1)      | 18 (52.9)    | 1 (100)         | 3 (30)                  | <.001       |
| Local Pain | 114 (30.9)     | 57 (41)                                | 43 (23.2)      | 11 (32.4)    | 1 (100)         | 2 (20)                  | .01         |
| Swelling   | 25 (6.8)       | 14 (10.1)                              | 9 (4.9)        | 2 (3.0)     | 0 (0)           | 0 (0)                   | .37         |
| Erythema   | 6 (1.6)        | 3 (2.2)                                | 3 (1.6)        | 0 (0)       | 0 (0)           | 0 (0)                   | .91         |
| Systemic   |                |                                       |               |             |                 |                         |             |
| Fever      | 21 (5.7)       | 5 (3.6)                                | 14 (7.6)       | 1 (2.9)     | 0 (0)           | 0 (0)                   | .52         |
| Headache   | 62 (16.8)      | 23 (16.5)                              | 31 (16.8)      | 7 (20.6)    | 1 (100)         | 0 (0)                   | .12         |
| Myalgia    | 86 (23.3)      | 38 (27.3)                              | 38 (20.5)      | 10 (29.4)   | 0 (0)           | 0 (0)                   | .19         |
| Fatigue    | 98 (26.6)      | 47 (33.8)                              | 40 (21.6)      | 11 (32.4)   | 0 (0)           | 0 (0)                   | .03         |
| Nausea/    | 25 (6.8)       | 14 (10.1)                              | 10 (5.4)       | 1 (2.9)     | 0 (0)           | 0 (0)                   | .34         |
| Vomiting   |                |                                       |               |             |                 |                         |             |
| Diarrhea   | 26 (7.1)       | 15 (14.7)                              | 11 (6.8)       | 1 (2.9)     | 0 (0)           | 1 (10)                  | .25         |
| Arthralgia | 18 (5.0)       | 8 (5.3)                                | 7 (3.8)        | 3 (8.8)     | 0 (0)           | 0 (0)                   | .66         |
| Back pain  | 14 (3.8)       | 9 (6.3)                                | 3 (1.6)        | 2 (5.9)     | 0 (0)           | 0 (0)                   | .20         |
| Dizziness  | 20 (5.4)       | 11 (7.9)                               | 8 (4.3)        | 1 (2.9)     | 0 (0)           | 0 (0)                   | .53         |

VRAE, vaccine-related adverse event; CMT, chemotherapy; IO, immunotherapy.
vaccine-related deaths were reported.\textsuperscript{9,10} Fever was the only VRAE that led to interruption of the cancer treatment. Developing a fever after chemotherapy is a matter of concern for patients and physicians because it is an important sign of infection. In our cohort, the incidence of fever associated with ChAdOx1-nCoV-19 vaccine reactogenicity was 8.3\% and 5.7\% following the first and second dose, respectively, with a median onset of 1 day after vaccination, and median duration of 2 days. Grade 3 fever (39–40°C) was reported in only 0.5\% of cases. These findings may help oncologists educate and reassure cancer patients that VRAEs from the ChAdOx1-nCoV-19 vaccine are unlikely to affect their cancer treatment.

From our exploratory analysis, vaccine reactogenicity might correlate with immunogenicity after COVID-19 vaccination. Cancer patients with positive seroconversion after the first vaccination had a considerably higher risk of developing VRAEs than those with negative seroconversion. This finding is consistent with the result of the CANVAX study,\textsuperscript{34} which revealed that the presence of systemic reactogenicity was associated with a higher magnitude of immune response to the COVID-19 vaccine in cancer patients.\textsuperscript{34} In our study, the seroconversion rate in cancer patients was significantly lower than among the healthy controls, which could explain why cancer patients had a lower incidence of VRAEs following the first vaccination. However, this association lost its statistical significance in multivariate analysis in the first dose, and it did not remain in the second dose. This could be explained by the limited number of patients and the unknown proper serologic titer cutoff.

Figure 3. (a) Incidence of vaccine related adverse events on each day following the first vaccination in cancer cohort. (b) Incidence of vaccine related adverse events on each day following the second vaccination in cancer cohort.
Table 4. Factors associated with any vaccine related adverse events after first vaccination.

| Factors                          | Any VRAE (N = 252) | No VRAE (N = 147) | Univariate analysis | Multivariate analysis |
|---------------------------------|--------------------|-------------------|---------------------|-----------------------|
|                                | N (%)              | N (%)             | Odds ratio (95% CI) | p-value               | Odds ratio (95% CI) | p-value |
| Age (years)                     |                    |                   |                     |                       |                      |         |
| ≥65                             | 84 (33.3)          | 68 (46.3)         | ref                 |                       |                      |         |
| <65                             | 168 (66.7)         | 79 (53.7)         | 1.72 (1.13–2.61)    | .01                   | 2.78 (1.67–4.63)    | <.01    |
| Sex                             |                    |                   |                     |                       |                      |         |
| Male                            | 84 (33.3)          | 68 (46.3)         | ref                 |                       |                      |         |
| Female                          | 168 (66.7)         | 79 (53.7)         | 1.72 (1.14–2.61)    | .01                   | 1.43 (0.87–2.36)    | .16     |
| BMI                             |                    |                   |                     |                       |                      |         |
| ≥18.5                           | 219 (86.9)         | 123 (83.7)        | ref                 |                       |                      |         |
| Underweight (<18.5)             | 33 (13.1)          | 24 (16.3)         | 0.77 (0.44–1.37)    | .37                   | N/A                  |         |
| Comorbidity                     |                    |                   |                     |                       |                      |         |
| No                              | 132 (52.4)         | 82 (55.8)         | ref                 |                       |                      |         |
| Yes                             | 120 (47.6)         | 65 (44.2)         | 1.15 (0.76–1.73)    | .51                   | N/A                  |         |
| ECOG                            |                    |                   |                     |                       |                      |         |
| 0-1                             | 233 (92.5)         | 145 (98.6)        | ref                 |                       |                      |         |
| 2                               | 19 (7.5)           | 2 (1.4)           | 5.91 (1.36–3.79)    | .02                   | 7.36 (1.51–35.9)    | .014    |
| Staging                         |                    |                   |                     |                       |                      |         |
| Non-metastasis                  | 64 (25.4)          | 67 (45.6)         | ref                 |                       |                      |         |
| Metastasis stage                | 188 (74.6)         | 80 (54.4)         | 2.46 (.56–3.79)     | <.001                 | 1.81 (1.09–3.01)    | .02     |
| Type of treatment               |                    |                   |                     |                       |                      |         |
| Targeted/Endocrine therapy      | 121 (48)           | 32 (21.8)         | ref                 |                       |                      |         |
| Chemotherapy                    | 98 (38.9)          | 108 (73.5)        | 0.24 (0.15–0.39)    | <.001                 | 0.41 (0.2–0.89)     | .02     |
| Immunotherapy                   | 32 (12.7)          | 6 (4.1)           | 1.41 (0.54–3.67)    | .48                   | 1.99 (0.7–5.72)     | .20     |
| Chemotherapy + Immunotherapy    | 10 (0.4)           | 1 (0.7)           | 0.26 (0.02–4.34)    | .35                   | 0.94 (0.05–17.49)   | .96     |
| Radiation                       |                    |                   |                     |                       |                      |         |
| No                              | 236 (93.7)         | 127 (86.4)        | ref                 |                       |                      |         |
| Yes                             | 16 (6.3)           | 20 (13.6)         | 0.43 (0.22–0.86)    | .02                   | 0.42 (0.18–0.98)    | .04     |
| Concurrent steroid use          |                    |                   |                     |                       |                      |         |
| No                              | 164 (65.1)         | 52 (35.4)         | ref                 |                       |                      |         |
| Yes                             | 88 (34.9)          | 95 (64.6)         | 0.23 (0.19–0.45)    | <.001                 | 0.65 (0.32–1.31)    | .23     |
| Influenza vaccine within 28 days |                    |                   |                     |                       |                      |         |
| No                              | 234 (92.9)         | 144 (98)          | ref                 |                       |                      |         |
| Yes                             | 18 (7.1)           | 3 (2)             | 3.69 (1.07–12.75)   | .04                   | 2.54 (0.65–9.92)    | .18     |
| Site of injection               |                    |                   |                     |                       |                      |         |
| Left                            | 208 (82.5)         | 129 (87.8)        | ref                 |                       |                      |         |
| Right                           | 44 (17.5)          | 18 (12.2)         | 1.52 (0.84–2.74)    | .17                   | N/A                  |         |
| Seroconversion                  |                    |                   |                     |                       |                      |         |
| No                              | 84 (34.6)          | 64 (46.4)         | ref                 |                       |                      |         |
| Yes                             | 159 (65.4)         | 74 (53.6)         | 1.64 (1.07–2.51)    | .02                   | 1.16 (0.71–1.90)    | .56     |

VRAE, vaccine related adverse event; ref, reference; ECOG, Eastern Cooperative Oncology Group; PS, performance status; BMI, Body mass index.

In addition, our study showed that non-elderly, poor performance status and metastasis-stage patients were associated with a higher risk, whereas receiving chemotherapy or radiation was associated with a lower risk of developing VRAEs after the first vaccination. Younger age has previously been identified as a known factor related to an increased risk of COVID-19 vaccine-related adverse effects in the general population. Our results support this finding in cancer patients. Poor performance status in patients is usually caused by advanced-stage cancer. The symptoms of advanced cancer and VRAEs may be indistinguishable, and these patients were more vulnerable than those with no metastases and good performance status which may explain why these patients reported VRAEs more frequently. Concurrent steroid use was a protective factor in univariate analysis. A steroid is an anti-inflammatory medication that has been shown to reduce the immune response and COVID-19 vaccine reactivity. The most common reason for use of steroids in our cohort was for pre-medication since the prevalent chemotherapy regimens were platinum and anthracycline based. As a consequence, the majority of patients treated with chemotherapy also received steroids, resulting in lower incidence of VRAEs. Nevertheless, the concurrent steroid use was not an independent factor after adjusting the significant factors from univariate analysis in multivariate
Table 5. Factors associated with any vaccine related adverse events after second vaccination.

| Factors                        | Any VRAE N = 189 (%) | No VRAE N = 180 (%) | Univariate analysis | Multivariate analysis |
|-------------------------------|----------------------|---------------------|---------------------|-----------------------|
|                               |                      |                     | Odds ratio (95% CI) | p-value               | Odds ratio (95% CI) | p-value               |
| Age (years)                   |                      |                     | Ref                 |                       |                       |                       |
| ≥65                           | 68 (36)              | 77 (42.8)           | 1.33 (0.88–2.02)    | .18 N/A               |                       |                       |
| <65                           | 121 (64)             | 103 (57.2)          |                    |                       |                       |                       |
| Sex                           |                      |                     | ref                 |                       |                       |                       |
| Male                          | 58 (30.7)            | 85 (47.2)           |                    |                       |                       |                       |
| Female                        | 131 (69.3)           | 95 (52.8)           | 2.02 (1.32–3.09)    | .001 1.56             | (0.94–2.61)          | .08                   |
| BMI ≥18.5                     |                       |                     | ref                 |                       |                       |                       |
| Underweight (<18.5)          | 161 (85.2)           | 155 (86.1)          |                    |                       |                       |                       |
| Comorbidity                   |                      |                     | ref                 |                       |                       |                       |
| No                            | 97 (51.3)            | 96 (53.3)           | 1.1 (0.72–1.63)     | .70 N/A               |                       |                       |
| Yes                           | 92 (48.7)            | 84 (46.7)           |                    |                       |                       |                       |
| ECOG 0-1                      | 175 (92.6)           | 174 (96.7)          | ref                 | .09 N/A               |                       |                       |
| 2                             | 14 (7.4)             | 6 (3.3)             | 2.32 (0.87–6.18)    |                       |                       |                       |
| Staging                       |                      |                     | ref                 |                       |                       |                       |
| Non-metastasis                | 49 (25.9)            | 76 (42.2)           |                    |                       |                       |                       |
| Metastasis stage              | 140 (74.1)           | 104 (57.8)          | 2.09 (1.35–3.24)    | .001 0.92             | (0.53–1.61)          | .78                   |
| Treatment type                |                      |                     | ref                 |                       |                       |                       |
| Targeted/Endocrine therapy    | 92 (48.7)            | 51 (28.3)           |                    |                       |                       |                       |
| CMT                           | 75 (39.7)            | 112 (62.2)          | 0.37 (<.001)        | 0.67 0.25             | (0.23–0.58)          | (0.34–1.33)          |                       |
| Immunotherapy                 | 21 (11.1)            | 16 (8.9)            | 0.59 (<.001)        | 0.45 0.07             | (0.28–1.27)          | (0.19–1.06)          |                       |
| Chemotherapy + Immunotherapy  | 1 (0.5)              | 1 (0.6)             | 8.52 N/A            |                       |                       |                       |
| Radiation                     |                      |                     | ref                 |                       |                       |                       |
| No                            | 184 (97.4)           | 169 (93.9)          |                    |                       |                       |                       |
| Yes                           | 5 (2.6)              | 11 (6.1)            | 2.4 (0.82–7.0)      | .11 N/A               |                       |                       |
| Concurrent steroid use        |                      |                     | ref                 |                       |                       |                       |
| No                            | 134 (70.9)           | 107 (59.4)          |                    |                       |                       |                       |
| Yes                           | 55 (29.1)            | 73 (40.6)           | 0.6 (0.39–0.93)     | .02 1.41              | (0.71–2.80)          | .33                   |
| Site of injection             |                      |                     | ref                 |                       |                       |                       |
| Left                          | 151 (79.9)           | 158 (87.8)          |                    |                       |                       |                       |
| Right                         | 38 (20.1)            | 22 (12.2)           | 1.81 (1.02–3.20)    | .04 0.90              | (0.47–1.73)          | .76                   |
| Seroconversion                 |                      |                     | ref                 |                       |                       |                       |
| No                            | 12 (6.9)             | 10 (5.9)            |                    |                       |                       |                       |
| Yes                           | 163 (93.1)           | 159 (94.1)          | 0.85 (0.36–2.03)    | .72 N/A               |                       |                       |
| Any VRAEs after first dose    |                      |                     | ref                 |                       |                       |                       |
| No                            | 35 (18.5)            | 100 (55.6)          |                    |                       |                       |                       |
| Yes                           | 154 (81.5)           | 80 (44.4)           | 5.5 (3.44–8.88)     | <.001 2.74            | (1.59–4.73)          | <.001                 |
| Duration between first and    |                      |                     | ref                 |                       |                       |                       |
| second dose of vaccine        |                      |                     | 0.14 (<.001)        | 0.20 0.01             | (0.09–0.22)          | (0.11–0.36)          |                       |
| 8 weeks                       | 153 (81)             | 67 (37.2)           |                    |                       |                       |                       |
| 10 weeks                      | 36 (19)              | 113 (62.8)          |                    |                       |                       |                       |

VRAE, vaccine related adverse event; ref, reference; ECOG, Eastern Cooperative Oncology Group; PS, performance status; BMI, Body mass index.

analysis. It is possible that the patients treated with chemotherapy or radiation had decreased immunogenicity on their own, which resulted in lower vaccine reactogenicity. It is noteworthy that all significant associated factors following the first dose did not show statistical significance following the second dose. This was most likely due to the lower incidence of VRAEs after the second vaccination.

To the best of our knowledge, this is the first prospective study to report the safety of the ChAdOx1-nCoV-19 vaccine in solid malignancy patients receiving cancer treatment compared to age matched healthy controls. We had a good number in the cancer cohort and enrolled patients who were treated with any systemic cancer treatment including chemotherapy, targeted therapy, biological agents, hormonal therapy and
immunotherapy. Among the cancer treatment types, patients undergoing chemotherapy-containing regimens had a lower likelihood of experiencing almost every VRAE. The rate of COVID-19 infection in cancer patients was about 4% during the study period. No one required ventilator support, and there were no reported deaths due to COVID-19 infection. Our results confirmed that the benefit of the COVID-19 vaccine outweighs the risk of adverse events.

There were several limitations to our study. First, most VRAEs overlap with side effects from cancer treatment, so patients might not be certain whether the occurring adverse events were related to the vaccine or not. This could lead to underreporting or overreporting of VRAEs in the cancer cohort. Second, when we used age-matched analysis to compare the incidence of VRAEs between cancer patients and healthy volunteers, the number of participants in each cohort...
decreased. That might have affected the power to detect statistical differences. However, the overall incidence of VRAEs in each cohort was nearly the same in the aged match comparison. Third, we used the seroconversion rate to represent the immunogenicity in our exploratory analysis, in spite of the fact that an appropriate cutoff of serologic titers is still unknown. Finally, the time of enrollment and follow-up for cancer patients and healthy controls were not parallel, which might have contributed to some bias.

Conclusions

The overall incidence of VRAEs in actively treated patients with solid malignancy following the ChAdOx1-nCoV-19 vaccine was comparable to healthy controls in age-matched comparison. The majority of VRAEs that did occur were of mild severity and rarely interrupted cancer treatment. Our findings are useful to health-care professionals who aim to convince cancer patients to be more comfortable with the COVID-19 vaccine during cancer treatment and decrease vaccine hesitancy. Moreover, it might help oncologists better understand the pattern and natural course of VRAEs, allowing them to handle COVID-19 vaccination during cancer treatment more properly.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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