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COVID and cancer

Covid Antibody Titers in Cancer Patients Following Vaccination with ChAdOx1 nCOV-19 Vaccine

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Abstract


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Covid-19 has led to significant mortality worldwide, with an increased risk in cancer patients. Vaccination provides significant protection against the infection. The study focuses on the immunogenicity and effectiveness of ChAdOx1 nCoV-19 vaccine in cancer patients within a real-world setting. Blood samples for measuring Covid antibody titers against the receptor binding domain were collected according to a convenient sparse sampling strategy in a real-world setting, with the days of the collection coinciding with their hospital appointment. The antibody titers between different groups were analyzed descriptively. A total of 56 patients were enrolled in the study. There was no apparent effect in antibody titers between patients with solid tumors and hematological malignancies (mean ± standard deviation [SD]: 36.80 ± 41.18 vs. 52.02 ± 26.27), among patients who were undergoing chemotherapy, immunotherapy, or local therapy (mean ± SD: 42.50 ± 44.46 vs. 50.06 ± 51.39 vs. 28.70 ± 25.03), and in patients with up to 90 days and more than 90 days' interval between their last treatment and date of vaccination (mean ± SD: 38.96 ± 42.66 vs. 40.51 ± 38.65). Additionally, there were only 2/56 patients with breakthrough infection, which points out the effectiveness of this vaccine in cancer patients. The ChAdOx1 nCoV-19 vaccine has activity in cancer regardless of the tumor type, type of treatment, or time from the last treatment.

Keywords

- ChAdOx1 nCoV-19
- Covid-19
- cancer
- Covid antibody
- Covishield

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Introduction

The Oxford-AstraZeneca (ChAdOx1) nCOV-19 vaccine is a recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV2 spike glycoprotein.[1,2] A pooled interim analysis of four randomized controlled trials and a phase 1/2 study showed that the vaccine had an acceptable safety and immunogenicity against the SARS-CoV-2 virus leading to its emergency use authorization in the United Kingdom.[3,4] In India, the ChAdOx1 nCOV-19 vaccine is manufactured and marketed by Serum Institute under the trade name Covishield. This vaccine was approved for use in India for adults older than 45 years with comorbidities in March 2021 and all adults above the age of 18 years in May 2021.[2] As of September 2022, a total of 2,175,667,942 doses have been administered (including the precautionary third dose) in India.[5] There are limited data on the safety and efficacy of these vaccines in cancer patients, primarily because cancer patients are usually excluded from these trials. Therefore, we decided to look at the safety and efficacy data of the ChAdOx1 nCOV-19 vaccine in cancer patients reporting to the Tata Memorial Hospital, Mumbai, in a prospective observational study.

In view of the increased morbidity and mortality due to COVID-19 in cancer, leading oncology groups like ESMO (European Society for Medical Oncology) and several others laid down guidelines to encourage complete vaccination in cancer patients.[6,7] However, the optimal timing of the vaccine in view of the patient's ongoing treatment was unknown. While the COVID-19 vaccine can be taken with cytotoxic chemotherapies, caution was warranted in case of immune checkpoint inhibitors.[8] Seroconversion is already low in cancer patients than in healthy individuals, more so in patients with hematological malignancies as compared to those with solid tumours.[9] Understanding the exact time of waning immunity is crucial in determining an optimal vaccination schedule for these patients. If patients who are not sufficiently protected by the conventional two-dose vaccination strategy, the addition of a third dose can be beneficial in increasing the immunity against COVID-19. Antibody (Ab) titers can be a useful tool in assessing this immunity and understanding the protective action of the current vaccination strategy in these patients.

This study focuses on the protective impact of a two-dose vaccination schedule of the Covishield vaccine in cancer patients using Ab titer values and the incidence of breakthrough infection.

Material and Methods

Study design, patients, and setting: Adult patients, older than 18 years with confirmed histological or cytological diagnosis of cancer who have received at least one dose of the ChAdOx1 nCOV-19 vaccine at Tata Memorial Hospital, Mumbai, were included in the study. Patients who could not recall the details of their vaccination (date and time) were excluded from the study. The baseline demographic, treatment, and Covid vaccination details of all participants were recorded.

Blood sample collection and processing: A 3-mL EDTA blood sample of the participants were collected serially at any of the following time points, namely, days 7, 14, 28, 35, 42, 56, 90, 120, and 180 after the first dose. Since this was a real-world evidence study, a convenient sparse sampling strategy was employed where participants were allowed to choose to give their blood sample, as per the time points mentioned earlier, on days coinciding with their hospital appointments. The blood samples were centrifuged at 3,000 rpm for 10 minutes. The supernatant plasma was collected and stored in prelabeled 1.7-mL microcentrifuge tubes at –20°C pending further analysis.

Ab titer analysis: Plasma samples of study participants were analyzed for Ab titer using a one-step antigen sandwich immunoassay (COV2T; Siemens Healthcare Diagnostic Inc, Tarrytown, New York, United States) on Atellica fully automated immunoassay analyzer. The Atellica IM COV2T assay is a fully automated one-step antigen sandwich immunoassay using acridinium ester chemiluminescent technology, in which antigens are bridged by Abs present in the sample. The Solid Phase contains a preformed complex of streptavidin-coated microparticles, and biotinylated SARS-CoV-2 spike 1 receptor binding domain (S1 RBD) recombinant antigens. This reagent is used to capture anti-SARS-CoV-2 Abs in the sample. The Lite Reagent contains acridinium-ester-labeled SARS-CoV-2 recombinant S1 RBD antigens used to detect anti-SARS-CoV-2 Abs bound to the Solid Phase. A direct relationship exists between the amount of SARS-CoV-2 antibodies present in the sample and the results reported in Index Units with <1.0 Index reported as nonreactive, ≥ 1.0 Index as reactive for the presence of antibodies. The linearity of the assay is 0.60 to 75.00 Index. Samples with values more than 75 were further diluted with Atellica IM Multi-Diluent 2, and results were calculated with appropriate dilution factors.

Breakthrough Covid infection: The participants were actively followed up for a median of 21 days after the first dose to gather information on breakthrough Covid infection. Breakthrough infection was defined as reverse transcription polymerase chain reaction (RT-PCR) positive for SARS-CoV-2 at least 21 days after the first dose of the vaccine.

Statistical analysis: Descriptive data were expressed as mean and standard deviation. All statistical analyses were carried out on GraphPad Prism version 7.04 for Windows (GraphPad Software, San Diego, California, United States).

Results

Baseline Characteristics

From July 2021 to April 2022, a total of 56 patients were enrolled in the trial. Their baseline demographics are outlined in ►Table 1. The majority of the patients were males with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 1. Solid tumors made up for almost 84% of the participant pool. In all, 24/56 (42.85%) patients had not taken their second dose of the Covishield vaccine, 12/56 (21.42%) patients had ongoing chemotherapy when they received their first dose of the vaccine, while 18

Table 1 Baseline characteristics of all patients ($n = 56$)

Sex	Male = 31 Female = 25
Age (y)	48.44 ± 13.21
ECOG PS	0 = 5 1 = 45 2 = 6
Type of cancer	Solid tumors = 47 Hematological malignancies = 9
Time between two vaccine doses (d)	120 ± 72
Time between the last chemo and vaccine dose (d)	103.97 ± 367.29
Ab titers	38.7 ± 39.6

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status.
Note: All values are expressed as mean ± SD.

(32.14%) patients were chemotherapy naïve when they received their first jab.

Antibody Kinetics in Cancer Patients:

The Covid Ab levels of all 56 patients are outlined in ►Table 2. In total, 51/56 (91.02%) patients were found to have neutralizing Abs at least at one time point from days 7 to 180. There was a rise in Ab levels from days 7 to 28, with the highest titers seen on day 28 (61.30 Index units), followed by a downward trend in Abs from days 42 to 180.

Interval between Last Chemotherapy and Antibody Titer

Patients on chemotherapy took the Covid vaccine as per their convenience. We analyzed the Ab titers in relation to administration of the last chemotherapy cycle. ►Fig. 1 shows a nonlinear curve fit (with 95% confidence interval [CI]) of Covid Ab titers in patients who had a difference of up to 90 days ($n = 26$) or more ($n = 12$) between their last treatment and their first dose of the vaccine. As seen from the figure, increased interval between chemotherapy administration does not lead to a substantial increase in Ab titer values (mean ± SD: 38.96 ± 42.66 vs. 40.51 ± 38.65).

Table 2 Antibody titers following vaccination in cancer patients

Day	Antibody titer in Index Units (mean ± SD)
7	6.39[a]
14	52.52 ± 41.77
28	61.30 ± 58.48
42	31.93 ± 25.95
56	18.27 ± 31.64
90	29.91 ± 28.70
120	13.13 ± 13.37
180	68.60 ± 44.17

[a]Since there was a single patient in the day 7 cohort, mean and standard deviation could not be calculated.

Tumor Type and Antibody Titer

We compared the Ab titers between different tumor types. ►Fig. 2 shows nonlinear curve fit (with 95% CI) of Covid Ab titers of patients with solid tumors and hematological malignancies (mean ± SD: 36.80 ± 41.18 vs. 52.02 ± 26.27). As observed, there is no significant difference between the Ab titer levels in patients with different tumor types.

Antibody Titers in Patients Undergoing Chemotherapy, Immunotherapy, and Local Therapy

►Fig. 3 shows a nonlinear curve fit (with 95% CI) of Covid Ab titers of patients undergoing chemotherapy, immunotherapy, and local therapy (mean ± SD: 42.50 ± 44.46 vs. 50.06 ± 51.39 vs. 28.70 ± 25.03). Thus, there was no significant difference in Covid Ab levels in patients irrespective of whether they were undergoing chemotherapy, immunotherapy, or local therapy.

Breakthrough Infections

Out of 56 patients enrolled in the trial, only 2 patients had a breakthrough infection. While a blood sample for one patient could not be collected, a 42nd-day sample of the second patient showed an Ab titer value of 12.16, which was almost three times less than the average titer values.

Discussion

Our study discusses the immunogenicity and efficacy of the ChAdOx1 nCOV-19 (Covishield) vaccine in cancer patients using Ab titer values. Our results do not show much difference in Ab levels between cancer patients with solid tumors or hematological malignancies, among patients whose chemotherapy was up to or more than 90 days from the first dose of the vaccine, and among the patient undergoing treatment with cytotoxic chemotherapy (or tyrosine kinase inhibitors [TKIs]) or immunotherapy. Additionally, only 2 of 56 patients had a breakthrough infection, which proves the efficacy of this vaccine in cancer patients.

Cancer patients as an immunocompromised group need to be prioritized in Covid vaccination policies by regulatory agencies. In addition, the systematic exclusion of these patients from most clinical trials focused on the safety and efficacy of myriad Covid vaccines makes real-world evidence studies like ours imperative. There is scarcity of serologic data from ChAdOx1 vaccine in Indian cancer patients. While studies have reported lower seroprevalence in cancer patients as compared to healthy volunteers, the Ab response increased after the second dose, leading to the U.S. Food and Drug Administration (FDA) to authorize emergency use of the booster dose for cancer patients.[2,10] Furthermore, patients with hematological malignancies have lower Ab levels as compared to patients with solid tumours.[10] However, our results suggest minimal difference in Ab titers with a (on the contrary) trend toward higher Ab levels in patients with hematological malignancies. This could possibly be due

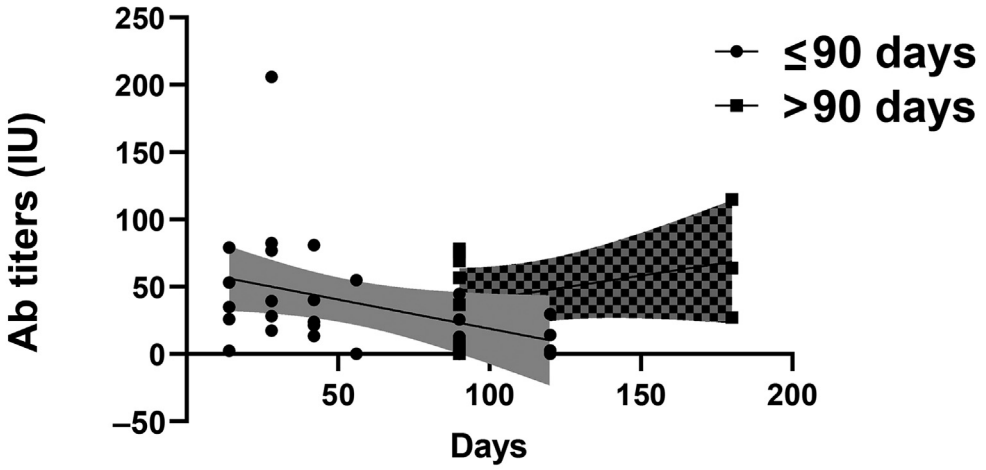

Fig. 1 Nonlinear curve fit of postvaccination Covid antibody titers of cancer patients across different time points for patients with up to and more than 90 days between their last chemo and Covid vaccination. The 95% confidence interval around the best fit line is shown. The *pattern-filled area* is the 95% confidence interval of patients with more than 90 days, while the *plain shaded area* is the 95% confidence interval of patients with up to 90 days between their last chemo and Covid vaccination.

to the small sample size of 9 patients versus 47 patients with solid tumors.

Covid Abs saw an upward trend from day 7, peaking at day 28, following which there was a fall in Ab titers, which were detectable until day 180. The highest titer was observed on day 28. This is in line with the results reported by Singh et al who found peak Ab titers from days 21 to 28 following by Covishield vaccination.[11] However, their study was conducted in healthy volunteers who had not had any prior Covid infection. Our study results also showed a high titer at day 180. This was due to a single patient's high value resulting from her second dose of the Covishield vaccine.

Another interesting finding of the study was that there was no significant difference in Ab titers in patients with an interval of 90 days or more between the last dose of chemotherapy administration and the first dose of the vaccine. This suggests that the vaccine can be administered safely in patients with ongoing treatment. Similarly, patients undergoing treatment with immunotherapeutic agents can also consider taking the vaccine with more confidence.

There is convincing evidence iterating the fact that cancer patients have lower immunogenicity than healthy volunteers. The study by Teeyapun et al compared the Ab titers between cancer patients and health volunteers following two doses of ChAdOx1 vaccine and found lower seroconversion rates of 60.8 and 78.9% after 4 and 8 to 10 weeks following the first dose and 93.6% after 4 weeks following the second dose as opposed to 97.1, 98.9, and 100%, respectively, in healthy volunteers.[12] This is also in line with our other data (unpublished) that show that cancer patients have lower Ab titers following the administration of the ChAdOx1 vaccine as compared to healthy volunteers. From the efficacy point of view, only 2 of 56 patients had Covid infection (confirmed by RT-PCR) within 21 days of taking their first

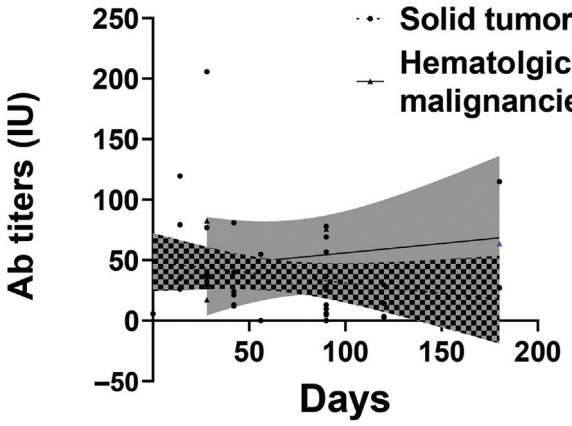

Fig. 2 Nonlinear curve fit of postvaccination Covid antibody titers of cancer patients across different time points for patients with solid tumors and hematological malignancies. The 95% confidence interval around the best fit line is shown. The *pattern-filled area* is the 95% confidence interval of solid tumors, while the *plain shaded* area is the 95% confidence interval of hematological malignancies.

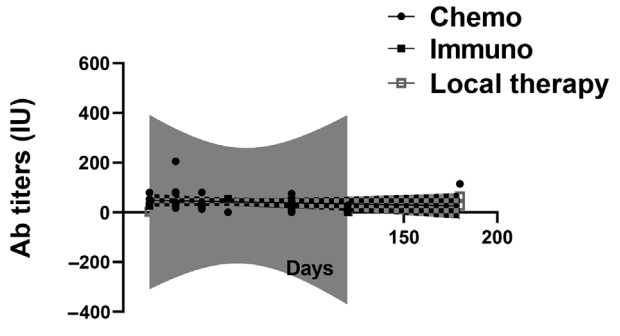

Fig. 3 Nonlinear curve fit of postvaccination Covid antibody titers of cancer patients across different time points for patients undergoing chemotherapy, immunotherapy, and local therapy. The 95% confidence interval around the best fit line is shown. The *pattern-filled area* is the 95% confidence interval of patients undergoing chemotherapy, while the *plain shaded* area is the 95% confidence interval of patients undergoing immunotherapy and local therapy.

dose. This is despite the occurrence of the third Covid wave in India that started in January 2022 and lasted till March 2022, which coincides with the observation period of our study. This establishes the efficacy of the vaccine in patients with cancer.[13] A low infection rate of 3.57% during the time when the virus spread was rampant points toward the efficacy of this vaccine in cancer patients.

Of the two patients who contracted Covid, one of the patient's samples could not be collected due to logistic issues. The second patient was a 41-year-old man with stomach cancer. The patient was diagnosed with cancer on October 16, 2021 and took the Covid vaccine on October 29, 2021, and his Ab sample was collected on December 10, 2021. The patient had not received any treatment when his sample was collected. His Ab levels were 12.16, which were almost three times lower than the average value of 38.7. The patient was diagnosed with Covid in January, 2022. This coincides with the trough Ab levels observed in our study and reported by other studies.

One limitation of the study was the selection of time points for Ab titer estimation. While this was a real-world experience, the sampling time points were based on convenience of the participants, making it unfeasible to look at the Ab kinetics in these patients.

To conclude, our study found that ongoing chemotherapy, of any kind, or the type of tumor does not have much effect on Covid Ab levels. This will encourage physicians and cancer patients to not delay their Covid jab in view of active cancer diagnosis or its treatment.

Authors' Contribution

AC was responsible for complete data collection and drafting of the manuscript. BS was involved in analyzing the data, drafting the manuscript, and preparing for publication. AS was involved in data collection. PC, UG, BP, and VB were responsible for analyzing the samples. CD and VG were involved in conceiving and designing the study, interpreting the data, and reviewing the manuscript critically. All the authors read and approved the final version of the manuscript.

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Conflict of Interest

None declared.

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Statement of Institutional Review Board Approval and/or Statement Conforming to the Declaration of Helsinki

The study was approved by the Ethics Committee of Tata Memorial Hospital, Mumbai, India. All trial participants provided written informed consent prior to their enrolment. The study was carried out in accordance with the Declaration of Helsinki and International Conference on Harmonization – Good Clinical Practice (ICH-GCP) guidelines.

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