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Comparison of immunogenicity for Sinovac-CoronaVac vaccine *vs.* natural infection during cancer treatment

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Abstract. – OBJECTIVE: Efficacy of the COVID-19 vaccines in cancer patients, especially during their active treatment, are lacking. Most of the studies in the literature compared the immunity in cancer patients with a cross-sectional cohort or retrospectively. Our study investigated Sinovac-CoronaVac COVID-19 vaccine immunogenicity and compared it with natural COVID-19 disease in cancer patients during their cancer therapy.

PATIENTS AND METHODS: A total of 111 patients with cancer and who are on active treatment were included in the study. This is a single-center study and was designed prospectively. Two group of patients were included in the study, natural disease and vaccinated group.

RESULTS: A total of 111 patients were included in the study, 34 of whom had natural COVID-19 disease. Antibody levels following the first dose vaccine were 0.4 (0-1.9) U/ml while after the second dose of vaccine were 2.6 (1.0-7.25) U/ml. Immunogenicity levels were 82.4% in the natural disease group and 75.8% in the vaccinated group after the second shot of the vaccine. Immunogenicity rate was significantly higher in non-chemotherapy (receiving immunotehrapy/targeted therapy or biologic agent) group compared to chemotherapy drug (92.9% *vs.* 63.3%, *p*=0.004). There was a difference between the antibody levels following the first and second vaccination [median (IQR): 0.3 (0-1.0) and 3.3 (2.0-6.7), *p*=0.001, respectively].

CONCLUSIONS: The present study revealed that the Sinovac-CoronaVac vaccine showed an acceptable immunogenicity following two shots in cancer patients who were receiving active systemic therapy. On the other hand, natural disease immunogenicity was higher than vaccinated group.

Key Words:
COVID-19, Cancer, Chemotherapy, Immunogenecity.

Introduction

According to the WHO Coronavirus (COVID-19) dashboard[1], more than 4.5 million deaths were observed Worldwide, and more than 5 billion vaccine doses have been administered. The pandemic affected roughly all medical care as well as oncologic care. At the beginning of the pandemic, we did not know how to manage cancer patients, but now we can treat our patients with good experience and courage[2]. However, data about the efficacy and safety of the COVID-19 vaccines in cancer patients, especially during their active treatment, are lacking. There is a major concern about how cancer patients will achieve immunity if they get natural COVID-19 disease or vaccination[3]. A new study[4] from Israel found that chronic lymphocytic leukemia (CLL) patients had 39.5% of a positive immune response, and antibody response was only 16% in patients who were on active treatment following the BNT162b2 (Pfizer-BioNTech) messenger RNA (mRNA) vaccine. On the other hand, cancer patients with solid tumors showed a higher seroconversion rate (94.5% *vs.* 81.7%) compared to hematologic cancers[5]. Another study[6] investigated the immune response to COVID-19 vaccination during active cancer therapy and found lower immunity in cancer patients compared to noncancer controls.

Most of the studies[5,6] in the literature compared the immunity in cancer patients with a cross-sectional cohort or retrospectively and without a natural disease immunity arm with a similar control group. Our study investigated Sinovac-CoronaVac COVID-19 vaccine immunogenicity and compared

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it with natural COVID-19 disease in cancer patients during their cancer therapy.

Patients and Methods

This is a single-center and designed prospectively study. All patients with cancer and who were on active treatment were included in the study. Inclusion criteria were:

- The first group included patients diagnosed with COVID-19 disease during their active cancer treatment and admitted to the hospital because of COVID-19 disease.
- The second group included patients vaccinated with Sinovac-CoronaVac COVID-19 vaccine during their cancer treatment with two shots of it.

Exclusion criteria were:

- Previously diagnosed with COVID-19 disease or previous positive antibody results because of asymptomatic COVID-19 disease,
- Completed cancer therapy within three months of last control, and hematologic malignancies including lymphomas.

At the beginning of the study, the Sinovac-CoronoVac vaccine was the most common vaccine for oncology patients in Turkey. That is why we did not enroll the patients who received anything other than the Sinovac-CoronoVac vaccine. As characteristics, gender, age, cancer types and stages, chemotherapy regimens, vaccine times, and toxicity profiles were recorded. Blood samples were collected following the first and second vaccination after 3-4 weeks.

According to the study protocol, pharyngeal and nasal swab specimens were collected to diagnose patients in the first group for the real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) analysis. Patients' blood samples were collected after the first 3-4 weeks of each vaccine shot and stored at -80°C until the analysis.

Quantitative IgG Test

For quantitative IgG detection, ADVIA Centaur® SARS-CoV-2 IgG (Siemens, Washington, DC, USA) kits were used, and the immuno-enzymatic chemiluminescence method was used according to the manufacturer's recommendations. The test "quantitatively" detects IgG-type antibodies against the virus spike (S) protein receptor binding site (RBD). The detection range of the kit is 0.5-150 U/ml, and values above ≥1.00 U/ml are considered positive. In the manufacturer's user manual, the test's sensitivity is 96.4%, the specificity is 99.9%, and it was stated as 1 BAU/mL=21.8 U/ml, which is the standard unit recommended by WHO.

The study was approved by Sakarya University Medicine Faculty Ethical Committee and performed in accordance with the Helsinki Declaration (07.05.2021-16214662-050.01.04-28543-101).

Statistical Analysis

Data analysis was performed by using SPSS v. 22 for Windows (Statistical Package for Social Science, IBM Corp., Armonk, NY, USA). Visual (histograms, probability plot) and analytical (Kolmogorov-Smirnov/Shapiro-test) Wilk's methods were used to evaluate if the variables were nırmaly distributed. Continuous variables were reported as the median and interquartile range (IQR) and as whole numbers and percentages for categorical variables. Variables that were not normally distributed were compared using the Kruskal-Wallis' test. We used a mixed model ANOVA on the before and after dependent values. In addition, the Mann-Whitney U test was used to compare continuous nonparametric variables. The Chi-square test was used to compare the proportions in different groups. The statistically significant two-tailed *p*-value was considered as <0.05.

Results

A total of 111 patients were included in the study, 34 of whom had natural COVID-19 disease and were located in group 1. All 77 vaccinated patients received two shots of the vaccine at 4-5 weeks intervals. In addition, on the 4-6th months, late antibody testing was performed in nine of the patients who received the double dose vaccine. Vaccinated and naturally immunized patients were compared in terms of age, and there was a significant difference [median (interquartile range=IQR): 69 (65-75) *vs.* 56 (48-66.5), respectively, $p<0.001$]. However, there was no difference between the groups in terms of gender distribution ($p=0.061$), body mass index (BMI) value ($p=0.470$), primary cancer diagnosis ($p=0.116$), disease stage (p=0.782), and smoking status ($p=0.964$) (Table I). Further, when compared in terms of mortality, death occurred in 4 patients (11.8%) in the innate immunity group, while it occurred in only 1 patient (1.3%) in the vaccine group ($p=0.014$). In the vaccine group, 15 of 77 patients received 5-Fluorouracil, 13 patients

Table I. General characteristics of the patients included in the study.

	Vaccine immunity (n=77)	Natural immunity (n=34)	*p*-value
Age, years	69 (65-75)	56 (48-66.5)	**<0.001**
Gender, F/M (%)	48/29 (62.3/37.7)	14/20 (41.2/58.8)	0.061
BMI, kg/m2	27.3 (23.6-30.1)	28.4 (22.4-32.5)	0.470
Cancer types, n (%)			
Non-small cell lung cancer breast cancer	17 (22.1)	6 (17.6)	0.116
Small cell lung cancer breast cancer	3 (3.9)	3 (8.8)	
Breast cancer	8 (10.4)	11 (32.4)	
Colorectal cancer	21 (27.3)	7 (20.6)	
Prostate cancer	7 (9.1)	0	
Gastric cancer	2 (2.6)	0	
Pancreaticobiliary cancer	5 (6.5)	0	
Esophageal cancer	1 (1.3)	0	
Bladder cancer	2 (2.6)	0	
Kidney cancers	2 (2.6)	1 (2.9)	
Head and neck cancer	4 (5.2)	2 (5.9)	
Endometrial cancer	2 (2.6)	1 (2.9)	
Ovarian cancer	3 (3.9)	1 (2.9)	
Cervical cancer	0	1 (2.9)	
Others	0	1 (2.9)	
Stage, n (%)			
Early-stage	9 (11.7)	5 (14.7)	0.782
Locally advanced stage	20 (26.0)	7 (20.6)	
Metastatic stage	45 (58.4)	21 (61.8)	
Missing data	3 (3.9)	1 (2.9)	
Treatment			
Cytotoxic chemotherapy	50 (64.9)	23 (67.6)	0.450
Hormonotherapy	3 (3.9)	-	
Monoclonal antibody therapy	1 (1.3)	-	
Immunotherapy	2 (2.6)	-	
Targeted therapy	3 (3.9)	-	
No treatment	18 (23.4)	11 (32.4)	
Smoking, n (%)			
Yes	23 (29.9)	10 (29.4)	0.964
No	31 (40.3)	13 (38.2)	
Quit smoking	23 (29.9)	11 (32.4)	
Mortality, n (%)	1 (1.3)	4 (11.8)	0.014

were treated with taxane-based therapy, 12, 8 and 7 patients received oxaliplatin, carboplatin, and cisplatin respectively, 8 patients received gemcitabine, 4 patients received vinorelbine and another 4 patients were treated with capecitabine, and other drugs were pemetrexed, irinotecan, temozolomide, nivolumab, and CDK4/6 inhibitors.

Antibody levels following the first dose vaccine were 0.4 (0-1.9) U/ml and after the second dose of vaccine was 2.6 (1.0-7.25) U/ml. On the other hand, antibody levels in the first group which was immunized by natural disease were 16.0 (2.5-106.8) U/ml and a significant difference was observed between the groups ($p<0.001$) (Figure 1). Immunogenicity levels were 82.4% in the natural disease group and 75.8% in the vaccinated group after the second shot of the vaccine. Following the first shot of the vaccine, 33 patients did not show immunogenicity, and following the second shot of vaccine 66% of them had positive antibody levels and showed immunogenicity after the second shot of vaccine. Immunogenicity rate was significantly higher in non-chemotherapy group (receiving immunotehrapy/targeted therapy or biologic agent) compared to chemotherapy drug (92.9% *vs.* 63.3%, $p=0.004$).

In nine patients who received two shots of vaccine, antibodies were measured in three different periods, both after vaccination and in the late period (4-6 months after the first vaccination). There was a difference between the antibody levels following the first and second vaccination [median (IQR): 0.3 (0-1.0) and 3.3 (2.0-6.7), $p=0.001$, respectively], also we found a significant decrease at the third measurement of antibody levels in the late term [median (IQR): 1.2 (1.0-1.7), $p=0.014$] (Figure 2).

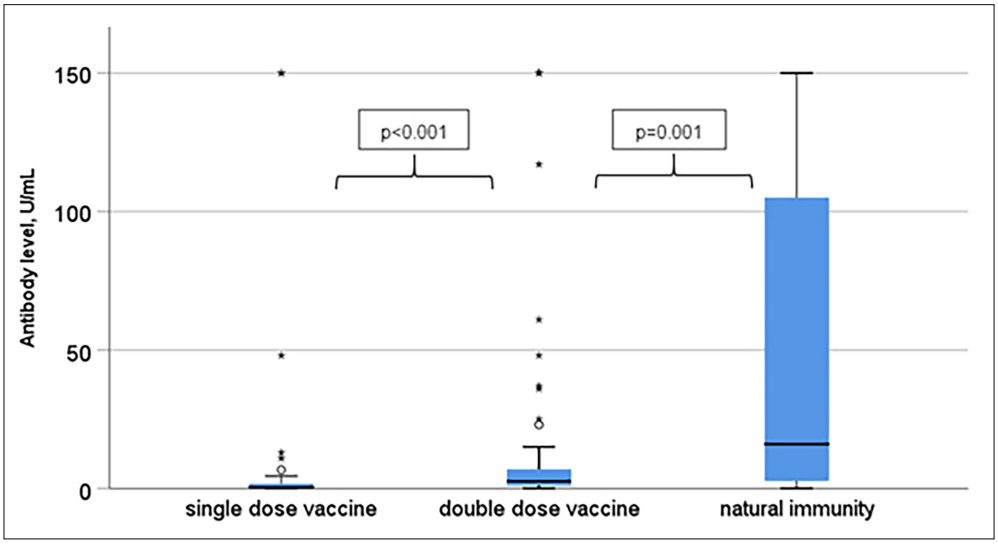

Figure 1. Comparision of antibody levels.

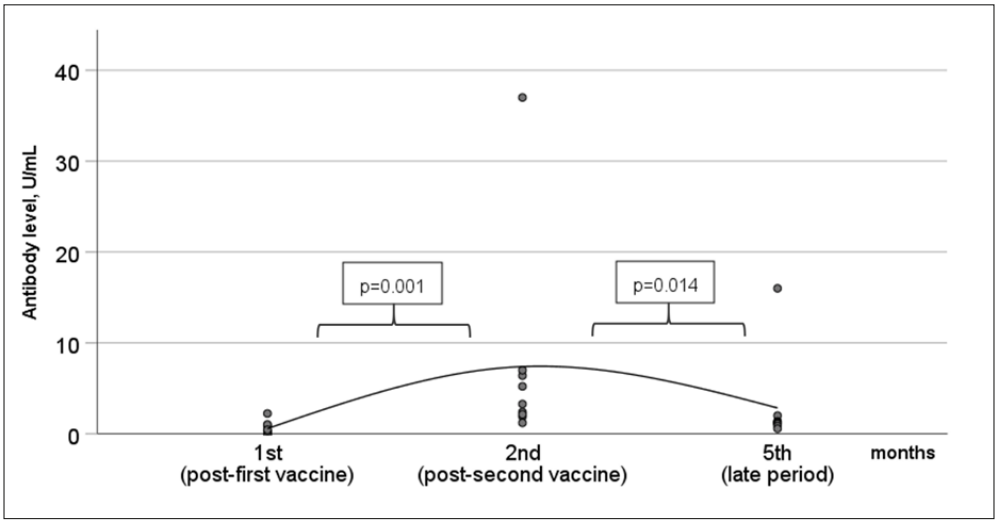

Figure 2. Change in antibody levels over time.

Vaccinated patients were compared in terms of antibody levels according to whether they received chemotherapy or not [with/without chemotherapy (n=49/28)], and there was no significant difference (p=0.110). Likewise, the natural immunity group was compared in terms of antibody levels according to whether or not they received chemotherapy [with/without chemotherapy (n=26/8)], and there was no significant difference (p=0.662). Further, we did not find a significant correlation between antibody titers between age (r=-0.136, p=0.155), and BMI (r=0.113, p=0.269). Lastly, antibody levels were also compared between smokers, ex-smokers, and non-smokers, and no significant difference was observed (p=0.327).

Lastly, for the follow-up period before the submission of the manuscript, none of the patients had COVID-19 disease in the vaccine group and none of them had a second infection in the natural disease group.

Discussion

The current study revealed that patients with active cancer showed immunogenicity during anti-cancer therapy following the Sinovac-CoronaVac COVID-19 vaccine. Immunity started after the first vaccination but following the second shot, it reached peak value. On the other hand, the Sinovac-CoronaVac COVID-19 vaccination immunity could not reach the same values as that following the natural disease immunity. Treatment type as a cytotoxic drug, immunotherapy, targeted therapy, or single agent vs. doublet therapies did not significantly affect the immunity.

It is widely acknowledged[7] that cancer patients undergoing antineoplastic therapy should be given priority for vaccination. In our country, the Sinovac-CoronaVac COVID-19 vaccine was the first approved vaccine by our health authority, so we chose this vaccine for the study enrollments. BNT162b2 (Pfizer-BioNTech) is a lipid-based nanoparticle vaccine that was modified as an RNA technology and it has a plausible safety profile with a 95% efficacy rate to prevent COVID-19. The clinical trial data[8] for BNT162b2 included medically fit or chronically ill participants. However, patients who were on immunosuppressive treatment for cancer treatments were excluded. It has been accepted that cancer patients prioritized COVID vaccination, but the ideal timing of it was not determined. The Centers for Disease Control and Prevention (CDC)[9,10] concluded that 2 weeks before cancer therapy is appropriate for the oncology population, but it is not possible for many cancer patients who were on active therapies. A recent study[11] investigated BTN162b2 mRNA efficacy in patients treated for cancer. Agbarya et al[11] measured humoral response of BTN162b1 in 140 patients following the second shot of vaccination and they found that 14.3% of 140 patients did not have immunogenicity following the vaccination. The control group of the study showed that 1.4% did not develop antibodies in 215 healthy controls. Also, the median IgG levels of SARS-CoV-2 were significantly lower in cancer patients (median 2,231 AU/mL *vs.* 4,100 AU/mL, p=0.001). In addition, 73 patients who were treated with active chemotherapy showed[11] significantly higher seronegativity compared to 67 non-chemotherapy cancer patients and 215 healthy controls (23.3% *vs.* 4.5% *vs.* 1.4%, p<0.001). The median IgG levels were also lower in this subgroup (1,361 AU/mL *vs.* 4,100 AU/mL, p<0.001)[11]. In our study, we measured antibody levels in each step including before and intervals of vaccine shots and we showed that the Sinovac-CoronaVac vaccine achieved an acceptable immunogenicity rate of 75.8%. In addition, the natural immunogenicity rate was non-significantly higher than the vaccinated group (82.4% *vs.* 75.8%, p=0.41) but antibody levels were significantly higher after natural disease compared to the Sinovac-CoronaVac vaccine. One of our novel findings was the investigation of the natural immunogenicity in cancer patients only receiving active treatment and compared with a vaccinated same patient profile. Another recent study published by Ligumsky et al[12] measured the immunogenicity of 326 patients with solid tumors during active therapy. Similar to previous study results[12], seronegativity was significantly higher in the chemotherapy group compared to the healthy control (11.9% *vs.* 3%, p=0.001). The seronegativity proportion was higher in the chemotherapy-treated group (18.8%) and decreased in the groups in ICI-treated patients (9.1%) and those treated with targeted therapy (2.6%) (p=0.02).

A recent study published by Karacin et al[13] and investigated the immunogenicity of the CoronaVac vaccine in patients with cancer during active systemic therapy. Totally they measured 47 patients' antibody levels before the first cycle of treatment and following the second shot of vaccine. The immunogenicity rate was around 64% (30/47) in the entire group, 60% (25/42) in those who received at least one cytotoxic drug, and 100% (5/5) in patients who received immunotherapy or monoclonal antibody alone[13]. This study was similar to our population but, we also measured the immunogenicity in the interval of vaccine shots and showed an increased pattern of antibody levels. Moreover, long-term measurement of immunogenicity in cancer patients showed a decreasing pattern of antibody levels so we should advise the third shot of vaccine on the 4-6th month of the second shot. Immunogenicity rate was numerically lower in chemotherapy group both in Karacin et al's study[13] and in our study with the Sinovac-CoronaVac compared to the Pfizer-BioNTech but, similar rates were found in immunnotherapy or biologic agents. According to this finding we can speculate that cancer patients who are being treated with cytotoxic drug should be vaccianted with mRNA-based vacicne, on the other hand both vaccines should be ordered to the patients who are being treated with immunotherapy, biologic agent or targeted therapies.

Conclusions

The present study revealed that the Sinovac-CoronaVac vaccine showed acceptable immunogenicity after two shots in cancer patients who received active systemic therapy. On the other hand, natural disease immunogenicity was higher in the same patient profile and after 4 months from the last shot, antibody levels dropped, therefore, we should recommend an extra shot of Sinovac-CoronaVac in cancer patients.

Ethics Approval

The study was approved by Sakarya University Medicine Faculty Ethical Committee and was performed in accordance with the Helsinki Declaration (07.05.2021-16214662-050.01.04-28543-101).

Informed Consent

Written informed consent was obtained from all patients before inclusion in the study.

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Authors' Contributions

Each Author has contributed substantially to the research, preparation and production of the paper and has approved of its submission to the Journal.

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Conflict of Interest

All authors declared that there is no potential conflict of interest relevant to this article.

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