Immunogenicity and Safety of CoronaVac Vaccine in Elderly Cancer Patients Receiving Cytotoxic Chemotherapy

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ABSTRACT

The aim of our study to evaluate the immunogenicity and safety of inactivated CoronaVac vaccine in elderly cancer patients actively receiving cytotoxic chemotherapy. This single-center, prospective cohort study was conducted with 42 patients older than 65 years receiving cytotoxic chemotherapy and 43 healthy volunteers. CoronaVac vaccine was administered to both groups as two doses (3 µg/day) on days 0 and 28. Antibody levels measured after 28 days (+/-3 days) from second dose of vaccine and ≥ 1 U/mL were considered positive. Antibody seropositivity was detected in all the controls (n= 43, 100%). Of the 42 patients, seropositivity was detected in 32 (76.2%) cases (p< 0.001). The median antibody level was significantly lower in the patient group than in the control group (21.6 U/ml vs 51.7 U/ml respectively, p= 0.011). SARS-CoV-2 infection was detected in five of the 42 cancer patients and none of the control group. None of the patients who tested positive for COVID-19 had pulmonary involvement, and none of the patients died due to SARS-CoV-2 infection. Despite of the developed poor immune response than healthy adults, CoronaVac vaccine was effective and safe in elderly cancer patients with actively receiving cytotoxic chemotherapy.

Keywords: Cancer, Chemotherapy, Elderly, COVID-19 vaccine, CoronaVac

INTRODUCTION

COVID-19 is a novel emerging infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Although it is characterized by atypical pneumonia, it can present with clinical manifestations ranging from mild or no symptoms to death.[1] As of December 2021, approximately 269 million confirmed cases of COVID-19 and approximately 5.3 million COVID-19 related deaths have been reported worldwide.[2] The risk of infection in immunocompromised patients, including cancer patients, is higher than in the general population. Due to chemotherapy-induced neutropenia, cancer patients have a greater risk of bacterial than viral infections.[3] Complications due to viral infections in immunosuppressed cancer patients leads to an increase in hospitalization and death rates.[4]

Despite the use of different treatment approaches, the optimal treatment for COVID-19 remains uncertain. Currently, vaccination is considered the best method to reduce COVID-19 related mortality.

As cancer patients were not included in SARS-CoV-2 vaccine development studies, information about the protection, side effects, and immunologic response to vaccination among cancer patients, especially those receiving chemotherapy, is insufficient. Despite the absence of data on SARS-CoV-2 vaccines for cancer patients, many international oncology societies have recommended that inactivated SARS-CoV-2 vaccines be administered to cancer patients receiving chemotherapy.[5-7] This prospective observational study aimed to compare the immunogenicity and safety of the COVID-19 vaccine CoronaVac (Sinovac Life Sciences, Beijing, China) in elderly cancer patients receiving cytotoxic chemotherapy with a control group.

PATIENTS AND METHODS

This single-center, prospective cohort study included patients aged older than 65 years who were not vaccinated before, had solid tumors, received cytotoxic chemotherapy, had no history of SARS-CoV-2 infection, and presented to Ondokuz Mayis University, Faculty of Medicine, Department of Medical Oncology between January 2021 and December 2021. Demographic data of all the included patients were recorded. Patients receiving targeted therapy or immunotherapy were not included in the study. The control group comprised healthy volunteers of similar ages without a diagnosis of cancer and not receiving immunosuppressive therapy. Informed consent was obtained from each patient included in the study. The protocol of the study was approved by the local ethics committee and the Ministry of Health.

Postvaccination, the patients were followed up. Side effects after the first and second doses of the vaccine were recorded in the patient and control groups, in addition to SARS-CoV-2 infection and mortality.

Vaccination Procedure

CoronaVac (Sinovac Life Sciences) vaccine was administered between two chemotherapy cycles when neutropenia was not detected. There was no intervention on the choice of vaccine in the patient and control groups. The first does of the vaccine (3 μg) was administered intramuscularly into the non-dominant arm. The second dose was administered 4 weeks after the first dose. Serum samples were taken 28 days after the second dose (+/-3 days) to measure the antibody level.

Serum Samples

Approximately 10 ml of venous blood were collected from each subject included in the study. Serum was separated by centrifugation at 5,000 rpm for 5 minutes within 2 hours after blood collection. Serum samples were collected in 1.5 ml Eppendorf tubes, and aliquots were stored at -20^{0}C until used analyzed.

Analysis of Serum Samples

All serum samples were analyzed using the Elecsys Anti-SARS-CoV-2 S (Roche Diagnostics, Pleasanton, CA, USA) electrochemiluminescent immunoassay on a Cobas e601 instrument (Roche Diagnostics, Basel, Switzerland). The Elecsys Anti-SARSCoV-2 S assay is a double-antigen sandwich assay designed for quantitative detection of total antibodies, including immunoglobulin G, against the receptor-binding domain (RBD) of the SARS-CoV-2 Spike protein and evaluation of the adaptive humoral immune response to this protein. In the evaluation of the results, samples with antibody levels of < 1 U/ml were considered negative, and those with antibody levels of ≥ 1 U/mL were considered positive. For samples above the upper analytical measurement range, dilutions were made using the diluent recommended by the manufacturer, according to the manufacturer's instructions.

Ethical approval was obtained from UKAEK Ondokuz Mayis University Clinical Research Ethical Comitee (Date: 24.03.2021 / No: 2021000180-1).

Statistical Analysis

Data were analyzed using IBM SPSS V23 (Chicago, USA) and Jamovi V2.2.5.0 (Sydney, Australia).[8,9] The conformity of the antibody levels to a normal distribution was evaluated by the Shapiro-Wilk test. The Mann-Whitney U test was used to compare quantitative data of the groups. The

Table 1. Demographhics, clinical and oncological features of the patients and controls

			Patients (n= 42)	**Controls** (n= 43)	**p**
Age, median (Range), y			70 (65 - 80)	70 (66 - 81)	0.968*
Gender, n (%)	Male		22 (52.4)	21 (48.8)	0.913**
	Female		20 (47.6)	22 (51.2)	
Comorbidity, n (%)	No		26 (61.9)	16 (37.2)	0.039**
	Yes		16 (38.1)	27 (62.8)	
		Hypertension	12 (75)	21 (77.8)	
		Diabetes Mellitus	6 (37.5)	9 (33.3)	
		Epilepsy	1 (6.3)	0 (0)	
		Ischemic heart disease	1 (6.3)	1 (3.7)	
		Congestive heart failure	1 (6.3)	0 (0)	NA
		Asthma	0 (0)	3 (11.1)	
		Dementia	0 (0)	2 (7.4)	
		Hipotyroidis	0 (0)	1 (3.7)	
		Cronic Obstructive Lung Desease	0 (0)	1 (3.7)	
Stage, n (%)					
2			2 (4.8)	---	NA
3			8 (19.0)	---	
4			32 (76.2)	---	
ECOG PS, n (%)					
0			14 (33.3)	---	NA
1			24 (57.1)	---	
2			4 (9.5)	---	
Cancer Type, n (%)					
Overian			8 (19)	---	
Colon			6 (14.3)	---	
Rektum			5 (11.9)	---	
Lung			4 (9.5)	---	
Gastric			4 (9.5)	---	NA
Breast			3 (7.1)	---	
Prostate			2 (4.8)	---	
Cervix			2 (4.8)	---	
Other			8 (19.2)	---	
Chemotherapy, n (%)					
Monotherapy			10 (23.8)	---	NA
Combined Therapy				32 (76.2)	---

** Mann Whitney U test; ** Continuity Correction, ECOG PS= Eastern Cooperative Oncology Group performance status*

Kruskal-Wallis test was used for comparisons of antibody titers according to Eastern Cooperative Oncology Group (ECOG) status and cancer stage, and the Dunn test was used for multiple comparisons. A robust one-way analysis of variance (ANOVA) was used to compare antibody values according to the group (experimental and control) and chronic disease (present or absent). Similarly, a robust one-way analysis of variance (ANOVA) was used to compare antibody values by group (experimental and control) and sex. Continuity correction and Fisher's exact test were used to analyze categorical data. The statistical significance level was $p < 0.05$.

RESULTS

Forty-two patients (males, n= 22, 52.4%; females, n = 20, 47.6%) with active cancer who were receiving chemotherapy in the oncology outpatient clinic were included in the study. The control group included 43 volunteers (males, n= 21, 48.8%; females, n= 22, 51.2%). The mean age of those in the patient group (min: 65, max: 80) and control group (min: 66, max: 81) was 70 years. There was no significant difference between the two groups in terms of age or gender (p= 0.968 and p= 0.913, respectively). The characteristics of the patient group and control group are shown in Table 1.

Table 2. Antibody titer of cancer patients compared with controls

	Patients (n= 42)		**Controls** (n= 43)		p
	Mean ± SD	**Median (min-max)**	**Mean ± SD**	**Median (min-max)**	
Antibody Titre	212.3 ± 801.9	21.6 (0.4 - 5000)	174.1 ± 391.2	51.7 (2 - 2318)	0.011[a]
Seropositivity, n (%)	32 (76.2)		43 (100)		< 0.001[b]

[a] *Mann Whitney U test;* [b] *Continuity Correction*

Antibody seropositivity was detected in all the controls (n= 43, 100%). Of the 42 patients, seropositivity was detected in 32 (76.2%) cases (p< 0.001). The median antibody value was 21.6 U/ml (min: 0.4, max: 5.000) in the patient group and 51.7 U/ml (min: 2, max: 2.318) in the control group (p= 0.011). The mean antibody value was higher in the patient group than in the control group because the antibody value was extremely high (> 5.000 U/ml) in one individual in the patient group (Table 2).

Descriptive statistics of median antibody levels by group, gender, and comorbidities are shown in Table 3. The median antibody levels in the patient group were higher in those with comorbidities than without comorbidities. In the control group, the antibody level was higher in those without comorbidities. In the patient and control groups, the median antibody level was higher in females than males (Table 3).

When the main effect of "group" on level was examined according to comorbidity or chronic disease, the effect was not statistically significant (p= 0.364 and p= 0.759, respectively). In addition, when the main effect of "group" on level was examined according to gender, the effect was not statistically significant (p= 0.261). Furthermore, the interaction effect of group × chronic disease and group × gender on antibody level was not significant (p= 0.112 and p= 0.609, respectively).

Median antibody level differed according to ECOG classifications (p= 0.015). The median antibody value was 9.2 in those with an ECOG score of 0, 27.8 in those with ECOG scores of 1 and 2, and 51.7 in the control group. There was a statistically significant difference in the antibody level of those with an ECOG score of 0 versus those in the control group (p= 0.017). There was no significant difference between those with ECOG scores of 1 and 2, and the control group and those with an ECOG score of 0 (p= 0.513 and p= 0.286, respectively). Although the median antibody level differed according to the cancer stage (Kruskal–Wallis test), this finding was not statistically significant based on the pairwise comparison using the Dunn test. Similarly, although the median antibody level differed according to monotherapy or combined therapy (Kruskal-Wallis test), the pairwise comparison using the Dunn test revealed no significant difference between monotherapy, combined therapy and control group.

Table 3. Descriptive statistics of antibody titers by groups, comorbidity and gender

	Ab titers, median (Min-Max)		
	Patients	**Controls**	**Total**
Comorbidity			
No	1.9 (0.4 - 5000)	73.1 (8.4 - 2318)	22.9 (0.4 - 5000)
Yes	52.7 (0.4 - 1661)	43 (2 - 1070)	43 (0.4 - 1661)
Total	21.6 (0.4 - 5000)	51.7 (2 - 2318)	37.6 (0.4 - 5000)
Gender			
Male	16.4 (0.4 - 5000)	50.6 (3.8 - 2318)	34.5 (0.4 - 5000)
Female	27 (0.4 - 198.1)	68.4 (2 - 1070)	41.1 (0.4 - 1070)
Total	21.6 (0.4 - 5000)	51.7 (2 - 2318)	37.6 (0.4 - 5000)

Table 4. Advers events (AE) related to vaccine

	Patients (n= 42)			**Control** (n= 43)			
	Grade 1,	**Grade 2**	**Total**	**Grade 1**	**Grade 2**	**Total**	**p***
First Dose, n (%)							
Total AE	4 (9.5)	10 (23.8)	14 (33.3)	9 (20.9)	10 (23.3)	19 (44.2)	0,557
Headache	2 (4.7)	4 (9.5)	6 (14.3)	1 (2.3)	3 (7.0)	4 (9,3)	
Local Pain	-	5 (11.9)	5 (11.9)	8 (18.6)	5 (11.6)	13 (30.2)	
Fatigue	2 (4.7)	-	2 (4.7)	-	-	-	
Fever	-	1 (2.4)	1 (2.4)	-	1 (2.3)	1 (2.3)	
Chill	-	-	-	-	1 (2.3)	1 (2.3)	
Second Dose, n (%)							
Total AE	3 (7.1)	9 (21.4)	12 (28.6)	5 (11.6)	12 (27.9)	17 (39.5)	0.391
Headache	2 (4.7)	2 (4.7)	4 (9.5)	1 (2.3)	2 (4.7)	3 (7.0)	
Local Pain	-	7 (16.7)	7 (16.7)	3 (7.0)	8 (18.6)	11 (25.6)	
Fatigue	1 (2.4)	-	1 (2.4)	1 (2.3)	-	1 (2.3)	
Fever	-	-	-	-	1 (2.3)	1 (2.3)	
Chill	-	-	-	-	1 (2.3)	1 (2.3)	

** Continuity Correction*

Four (9.5%) patients developed grade 1 side effects (headache, n= 2; fatigue, n= 2) after the first dose of the vaccine, and 10 (23.8%) patients developed grade 2 side effects (headache, n= 4; local pain, n= 5; fever, n= 1). Similarly, nine (20.9%) controls developed grade 1 side effects (headache, n= 1; local pain, n= 8) after the first dose of the vaccine, and 10 (23.3%) controls developed grade 2 side effects (headache, n= 3; local pain, n= 5; fever, n= 1; chill, n= 1). After the second vaccine dose, three patients (7.1 %) developed grade 1 side effects, and nine patients (21.4 %) developed grade 2 side effects. In the control group, the number of grade 1 and grade 2 side effects after the second dose of the vaccine was five and 12, respectively. When we compared the side effects that developed after the first and second doses of the vaccine in the patient and control groups, the results revealed no significant difference (p= 0.557 and p= 0.391, respectively) (Table 4).

SARS-CoV-2 infection was detected in five of the 42 cancer patients receiving chemotherapy during a median follow-up of 14 weeks and none of the control group during a median follow-up of 17 weeks. An antibody response was not detected in two of the patients. The antibody level was low (1.63) in one patient, and a positive antibody response (60.16 and 15.66, respectively) was found in two patients. In terms of chronic diseases, two patients had hypertension. Four patients had stage 4 disease, and one patient had stage 3 disease. All the five patients had different cancer diagnoses. One of the patients received chemotherapy as monotherapy, and the other four patients receiving combined chemotherapy. Only one patient with COVID-19 required hospitalization. While this patient was already hospitalized for her primary disease, she became covid 19 positive. None of the patients who tested positive for COVID-19 had pulmonary involvement, and none of the patients died due to SARS-CoV-2 infection.

DISCUSSION

Since the first report of SARS-CoV-2 in late 2019, the effects of the COVID-19 pandemic continue to be felt worldwide. Studies aimed at developing effective treatment methods are ongoing. To reduce mortality and protect against infection, the development of vaccines for COVID-19 has become important. A number of COVID-19 vaccines, including inactivated whole-virion vaccine CoronaVac (Sinovac Life Sciences), have been found to

be effective and safe for use in the general population.[10-12] In this study, we evaluated the efficacy and safety of the vaccine in elderly patients with cancer receiving cytotoxic chemotherapy.

Many international guidelines have recommended vaccination of immunocompromised patients, including cancer patients, to protect against SARS-CoV-2 infection. These recommendations are based on previous experience with influenza vaccinations, although there is no strong evidence that the benefits overweigh the potential risks of vaccinating cancer patients against influenza. According to reviews and meta-analyses, seroconversion and seroprotection are typically lower in cancer patients than general population. Nevertheless, a number of studies have reported a significant decrease in the duration and severity of influenza and associated morbidity and mortality in immunocompromised cancer patients who received the influenza vaccination.[13-15] In addition, there is no consistent evidence of disease progression or serious adverse events related to the influenza vaccination in these studies.

Studies have shown that older individuals (i.e., aged ≥ 60 years) with COVID-19 disease, especially those with chronic diseases, have an increased risk of worse outcomes and mortality compared with younger healthy individuals with COVID-19.[16,17] These Studies have also shown that elderly patients with COVID-19 disease tend to require intensive medical interventions and are frequently admitted to the intensive care unit Therefore, our study population, which comprised elderly patients diagnosed with cancer receiving cytotoxic chemotherapy, with potentially a reduced immune response, would have been expected to have a particularly high risk of severe SARS-CoV-2 infection.

Although not entirely clear, the antibody response to SARS-CoV-2 vaccines is thought to be associated with protection against infection and severe COVID-19 disease.[18] Recently published data revealed a correlation between the antibody response and disease prevention in healthy volunteers and patients with malignancies.[19,20] Due to the complexity of the immune response mechanism, simple serological tests for SARS-CoV-2 neutralizing antibodies may not reflect protective immunity against COVID-19. Along with the humoral immune system, antigen-specific T cells and cellular immunity are thought to play a central role in providing protection against COVID-19 and reducing the severity of the disease by promoting antibody production and directly killing virus-infected cells.[21-23] Nevertheless, the mechanisms of cellular immunity are not yet clearly defined. More comprehensive methods than serological detection of neutralizing antibodies are needed to shed light on the mechanisms underlying the response to SARS-CoV-2 vaccines.[24,25]

In this prospective study on the immunogenicity and safety of CoronaVac (Sinovac Life Sciences) vaccine in cancer patients aged > 65 years receiving cytotoxic chemotherapy, seropositivity was 100% in the control group compared to 76% in the patient group. The median antibody level was 51.7 U/ml in the control group and 21.6 U/ml in the patient group, with a statistically significant difference. These results are consistent with those in the literature on healthy controls and cancer patients receiving chemotherapy. In the first phase I-II trial of CoronaVac (Sinovac Life Sciences), the vaccine was administered to volunteers aged 18-59 years.[10] The vaccine was administered in doses of 3 μg or 6 μg in a two-dose schedule to two vaccination cohorts (0-14 days and days 0-28 days). Seroconversion of neutralizing antibodies was found in 92% and 98% of volunteers at doses of 3 μg and 6 μg, respectively (0-28-day schedule). Another phase I-II study evaluated the efficacy and safety of CoronaVac (Sinovac Life Sciences) in healthy individuals aged 60 years and older.[11] In this study, doses of 1.5 μg, 3 μg, or 6 μg were administered on days 0 and 28, and seroconversion rates were 90.7%, 98.0%, and 99.0%, respectively. In a phase III trial in Turkey, 10.214 healthy adults were randomized and assessed the efficacy of two doses of CoronaVac (Sinovac Life Sciences) vaccine in preventing symptomatic COVID-19 and COVID-19 disease-related hospitalization (12). According to the interim results, the efficacy of the vaccine in preventing symptomatic COVID-19 and COVID-19 disease-related hospitalization was 83.5% and 100%, respectively, at least 14 days after the second dose of the vaccine.[12] Also, this research reported that seropositivity decreases with increasing age. In a phase III study in Brazil that enrolled 9.823 healthy

adults, 14 days or more after the second dose of CoronaVac (Sinovac Life Sciences) vaccine, the efficacy of the vaccine in preventing symptomatic COVID-19 disease was 50.7%.[26] None of the aforementioned phase I, II, and III studies included patients with active cancer receiving immunosuppressive therapy or chemotherapy. Therefore, there are insufficient data on SARS Cov-2 vaccine efficacy in these patient populations. In a study by Karacin et al.[27], which included 47 patients who were actively receiving cancer treatment, after two doses of CoronaVac (Sinovac Life Sciences) vaccine, the immunogenicity rate was 63.8%. This study included elderly patients, and 89.4% of the patients had received at least one round of cytotoxic chemotherapy. The remaining patients had received monoclonal antibody treatment and immunotherapy. There was no healthy control group in this study.

In our study, after the first dose of the vaccine, grade 1/2 side effects were observed in 33.3% and 44.2% of those in the patient and control groups, respectively. After the second dose, grade 1/2 side effects were observed in 28.6% and 39.5%, respectively. The most common side effect was local pain. Grade 3 and 4 side effects and toxicity-related deaths were not observed in the patient and control groups. In a phase III study on healthy adults, 18.9% of those in a CoronaVac (Sinovac Life Sciences) vaccine group experienced side effects, with the most common side effects being fatigue and local pain.[12] In this study, no grade 4 side effects were reported. Another study on patients with active cancer receiving treatment reported grade 1 and 2 side effects postvaccination[27], as in our study and, 18.95% and 23.1% of patients experienced side effects after the first and second doses of the vaccine, respectively. Since the patients included in our study were those receiving chemotherapy, hematological parameters were not evaluated since vaccine-related hematological side effects could not be distinguished from chemotherapy side effects. Leukopenia, lymphopenia, thrombocytopenia and the development of acute leukemia due to mRNA vaccines has been reported and it has been stated that this may be related to the production of endogenous spike protein by mRNA vaccines and their cytotoxic effects and damage to hematopoietic stem cells.[28] Although such hematological side effects are rare, they may pose a disadvantage for mRNA vaccines compared to CoronaVac vaccine in vaccine preference.

The efficacy of all COVID-19 vaccines appears to decrease within a few months after vaccination.[29] There are two main reasons for this decrease: First, immunity wanes over time, which is most prominent in older individuals.[30] This effect is typically quantified using the amount of virus-specific antibodies as a surrogate. Second, newly emergent SARS-CoV-2 variants capable of evading immunity can drastically reduce vaccine efficacy.[31,32] Therefore, serial antibody measurements are needed to reveal changes in antibody levels in long-term follow-ups. In addition, comprehensive studies with long follow-up periods are needed to determine the optimum timing of recurrent vaccination and to determine appropriate vaccination schedules and maintenance doses for healthy adults and immunosuppressed patient groups.

A limitation of the present study was not measuring SARS-CoV-2 antibody levels prior to administration of CoronaVac (Sinovac Life Sciences) vaccine. However, the presence of a control group with the same characteristics as the patients and the inclusion of patients without a history of COVID-19 disease can reduce the negative effect of this limitation. The small number of patients and the short follow-up period are other limitations of this study.

In conclusion, based on our findings, CoronaVac (Sinovac Life Sciences) vaccine was effective and safe in this immunosuppressed patient population. We recommend elderly patients with active cancer receiving cytotoxic chemotherapy should be vaccinated to protect against COVID-19 disease and to reduce disease severity and hospitalization

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