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Serologic Response to SARS-CoV-2 Vaccine in Patients with Breast Cancer

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ABSTRACT

Background: Our study aimed to measure effectiveness of Anti-S1 RBD (receptor binding domain) IgG Antibody levels against SARS (severe acute respiratory syndrome) Cov-2 in breast cancer patients and compare them with healthy participants.

Methods: This prospective cross-sectional, single-center study was designed to evaluate Anti-S1 RBD IgG antibody levels following SARS-CoV-2 vaccination in 54 breast cancer patients and 56 healthy controls without cancer diagnosis.

Results: Anti-S1 RBD IgG antibody test was positive in 79.6% (43/54) of breast cancer patients, in 92.9% (52/56) of participants in the control group (p=0.054) and, 63.3% in breast cancer patients who were on chemotherapy+/- molecularly targeted therapy following at least two doses of vaccinations. Hybrid vaccination (use of two different types of vaccines) and more than two doses of vaccinations were associated with higher antibody titers both in patient and control groups. Median time to vaccination was 123 days (8-427) in the entire group and was significantly associated with antibody titer. Among breast cancer patients, type and frequency of vaccination, age and use of cytotoxic therapies were significantly associated with the magnitude of antibody response to SARS-CoV-2 vaccination in our study.

Conclusion: Breast cancer patients developed a lower antibody response to vaccination against COVID-19 in comparison to healthy subjects. Clinical and treatment related factors might help in tailoring future vaccination strategies for specific subsets of breast cancer patients.

Keywords: Breast cancers, COVID-19, Anti-S1 RBD IgG Antibody, SARS-Cov-2 vaccine.

Meme Kanseri Hastalarında SARS-CoV-2 Aşısına Karşı Oluşan Serolojik Yanıtın Gösterilmesi

ÖZET

Giriş/Amaç: Çalışmamızın amacı, meme kanseri hastalarında yapılan SARS Cov-2 aşılarına karşı gelişen Anti-S1 RBD (reseptör bağlama alanı) IgG antikor düzeylerini ölçmek, etkinliğini değerlendirmek ve sağlıklı grup ile karşılaştırmaktı.

Yöntemler: Bu prospektif kesitsel, tek merkezli çalışmada, 54 meme kanseri hastası ve 56 sağlıklı bireylere SARS-CoV-2 aşılamasını takiben Anti-S1 RBD IgG antikor düzeylerini değerlendirmek amacı ile yapıldı.

Bulgular: Anti-S1 RBD IgG antikoru düzeyi meme kanseri hastalarının %79,6 (43/54)'da pozitifti, kontrol grubunda bu oran %92,9 (52/56) (p=0.054) idi, kemoterapi ve /veya hedefe yönelik tedavi alan ve en az iki doz aşı olmuş grupta ise %63,3. İki farklı aşı tipinin kullanılması ve iki dozdan fazla aşılanma hem hasta hem de kontrol grubunda daha yüksek antikor seviyesi ile ilişkiliydi. Medyan aşılama süresi tüm grupta 123 gündü (8-427) ve bu durum antikor seviyesi ile önemli ölçüde ilişkiliydi. Bu çalışmada meme kanseri hastalarında, aşı türü, aşı yapılış süreleri, yaş, sitotoksik tedavilerin kullanımı SARS-CoV-2 aşısına karşı gelişen antikor cevabı ile anlamlı bir ilişki olduğu görüldü.

Sonuç: Meme kanseri hastalarında COVID-19 aşılarına karşı gelişen cevap sağlıklı kontrol grubuna kıyasla daha azdı.

Anahtar kelimeler: Meme Kanseri, COVID-19, Anti-S1 RBD IgG Antikoru, SARS-Cov-2 aşısı

COVID-19 global pandemic had devastating effects on many people. The effect was even more severe in immunosuppressed patients. Coronaviruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV) (1). The most common symptoms of COVID-19 infection are fever, cough and shortness of breath. The primary mode of transmission for the COVID-19 virus is through respiratory droplets and close contact (1). The virus can cause serious respiratory complications, including pneumonia, especially in elderly patients and those with pre-existing diseases such as cancer (1).

Both cancer and antineoplastic treatments can cause immunosuppression therefore patients with cancer are considered to have a significantly higher risk for COVID-19 infection (2). Several studies suggested that cancer patients with COVID-19 have poor clinical outcomes (3). Therefore, patients with cancer have been prioritized in COVID-19 vaccination programs globally. However, as they were excluded from pivotal vaccine studies, the data on efficacy or immune response to COVID-19 vaccines in cancer patients were limited to a number of small prospective cohort studies (4). Vaccines are needed to prevent coronavirus disease 2019 (Covid-19) and protect people who are at high risk for complications. BNT162b2 (Pfizer-BioNTech) vaccine is a lipid nanoparticle–encapsulated mRNA-based vaccine that encodes the prefusion stabilized full-length spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19 (5). Sinovac (CoronaVac) is a traditional inactivated virus vaccine against COVID-19. Since it is inactivated, the virus cannot replicate, but it keeps the surface spike protein intact to trigger an immune response for protection against the live virus in infected individuals.

It has been shown that there is a robust correlation between antibody titers and efficacy across seven different vaccines against SARS-CoV-2, higher titers were associated with higher vaccine efficacy, despite uncontrolled variables across the studies (6, 7). Vaccination can produce long lasting immunity and protect people from SARS-CoV-2 variants (8). It has been shown that antibody response is generally higher after second dose of COVID-19 vaccination (9). A third dose of vaccination has only been offered in organ transplantation and in severely immunocompromised patients (10, 11).

In Turkey, initial vaccination has been performed with Sinovac in January 2021, mRNA-based vaccine was available after May 2021. Health-care providers and older people (>65 years of age), patients with chronic diseases were prioritized in the vaccination strategy. Most people, including health care providers and patients with cancer had two initial Sinovac and then two subsequent doses of mRNA-based vaccine. Those people who did not receive Sinovac as their first vaccine, had three doses of mRNA-based vaccine when it was available for vaccination.

This study aims to assess the impact of vaccination against COVID-19 in breast cancer patients who were on different treatment modalities compared to a control group of participants without cancer.

Materials and Method

This single-center prospective cohort study was conducted to evaluate the efficacy of vaccination (with Sinovac or BioNTech or hybrid with both) in patients with breast cancer. Study population included breast cancer patients and healthy controls who had at least two vaccinations with one of the approved COVID-19 vaccine. All participants underwent serologic Anti-S1 RBD Antibody test. The plasma samples of all participants were collected and kept at -20 ºC until analysis at our Medical Laboratory. The Atellica ® IM SARS-CoV-2 IgG Assay was used to quantitate IgG antibodies including neutralizing antibodies against SARS-CoV-2 (Siemens Healthcare Diagnostics Inc., Tarrytown, USA). The SARS-CoV-2 IgG assay detects antibodies to receptor binding domain (RBD) of the S1 spike antigen. The analytical measurement interval is 0,50 – 150,00 U/ml (index). The result <1,00 U/ml is accepted as nonreactive whereas >1.00 U/ml as reactive. A quantitative correlation of Atellica ® IM SARS-CoV-2 IgG Assay versus 50% of Plaque Reduction Neutralization Test ($PRNT_{50}$) was determined by linear regression and Pearson correlation, demonstrating a strong relationship with the correlation coefficient of 0,810. Since 1:80 $PRNT_{50}$ is a common benchmark for significant neutralization titers in convalescent plasma, Atellica ® IM SARS-CoV-2 IgG Assay values of 7 U/ml produce PRNT50 titers greater than 1:80 dilution with a 100% PPV and 99% prediction interval of 1:83 – 1:270 (12, 13). Vaccination information and the history of COVID-19 infection were checked from the national health record database for both patients and control groups.

Statistical Analysis

Descriptive statistics are performed as median (minimum to maximum) for non-normal distributions,

number of cases and percentage (%) for nominal variables. Comparison of characteristics between two group was performed with chi-square for parametric and Mann-Whitney U test for non-parametric variables. A p-value of <0.05 was considered statistically significant. SPSS for Windows (v. 22; IBM Corp., NY, USA) was used to analyze the data.

Results

Between July 2021 and December 2021, 54 consecutive patients with breast cancer and 56 healthcare providers without cancer were enrolled. All participants were female. Clinical, treatment characteristics and vaccination schema of enrolled patients are summarized in table 1. Median age was older in the patient group in comparison to the control group (49 vs 46 years in the patient and control groups respectively). Thirty-one patients and 38 healthy participants were younger than 50 years of age in the patient and control group respectively. Hybrid vaccination was more common in the control group (85 %) compared to the patient group (57.4 %). Forty-three % patients with breast cancer and 14 % of participants in the control group had vaccination with either BioNTech or Sinovac. Anti-S RBD IgG antibody test was positive in 79.6% (43/54) of patients with breast cancer, and in 92.9 % (52/56) of participants in the control group which was numerically higher in the control group (p=0.054).

Median IgG levels were similar in the patient and the control groups. Hypertension was the most common chronic disease in both groups (12.5% in breast cancer patients and 8.8% in the control group). Time to test (TTT: median time from last vaccination to the date of blood sampling) was 123 days (8-427) in the entire study population, it was not significantly different between the patient and control groups, 107 days (8-247) for the patient group and 145 days (36-427) for the control group, it is defined as the period between the last vaccination and antibody testing. One participant in the control group was enrolled in the clinical study evaluating the efficacy of BNT162b2 vaccine). Smoking history and comorbidities rates were also similar between the patient and control groups.

In the patient group, 37 (68.5%) patients had early stage, and 17 (31.4%) had metastatic breast cancer. Thirty patients (55.6%) were on CT+/-targeted therapy, 24 (44.4%) were on HT+/- targeted therapy at the time vaccination and blood sampling. Among patients with breast cancer, age, type of therapy, time to test, type and frequency of vaccination were significantly associated with antibody response to vaccination in univariate analysis (Table 2). Among 31 patients who were on chemotherapy 19 (63%) had seropositivity following at least two doses of vaccination.

Table 1. Characteristics of study population

Characteristics	Total (n=110)	Patients (n=54)	Controls (n=56)	p-value
Seropositivity rate %	95 (86.4)	43 (79.6)	52 (92.9)	0.054
Age(years), median (range)	48 (30-77)	49 (36-77)	46 (30-69)	0.000
TTT, Median (range) days	123 (8-427)	107 (8-247)	145 (36-427)	0.078
IgG, Median (range) U/mL	101 (0-150)	76(0-150)	95 (2-150)	0.061
Age				
≤50 years	69 (62.7)	31 (57.4)	38 (67.9)	0.325
>50 years	41 (37.2)	23 (42.6)	18 (32.1)	
Smoking status				
Never smoker	24 (21.8)	15 (26.8)	8 (15.7)	0.069
Smoker	86 (78.1)	41 (75.9)	45 (80.3)	
Comorbidities				
Yes	27 (24.5)	16 (29.9)	11 (19.6)	0.259
No	83 (75.5)	38 (70.4)	45 (80.4)	
Type of vaccine				
Only BTN162b2	22 (20)	19 (35.2)	3 (5.4)	0.000
Only Sinovac	9 (8.2)	4 (7.4)	5 (8.9)	
Both of them	79 (71.8)	31 (57.4)	48 (85.8)	

**Abbreviations: TTT: time to test*

Table 2. Impact of clinical and treatment related factors on seropositivity in the patient group by univariate analysis

Parameters	Seropositive n (%)	Seronegative n (%)	p- value
Age			
≤50 years	21 (67.7)	10 (32.2)	**0.016**
>50 years	22 (95.7)	1 (4.3)	
Type of treatment			
CT +/- Targeted Th	19 (63.3)	11 (36.7)	**0.001**
HT+/- Targeted Th	24 (100)	0	
Smoking status			
Never smoker	23 (74.2)	8 (25.8)	0.319
Smoker	20 (87)	3 (13)	
Breast cancer stage			
Early	28 (75.7)	9 (24.3)	0.470
Metastatic	15 (88.2)	2 (11.8)	
Comorbidities			
Yes	5 (83.3)	1 (16.7)	0.708
No	1 (100)	9 (23.7)	
Type of vaccination			
Monotype vaccination (BTN162b2 or Sinovac)	12 (52.2)	11 (47.8)	**0.000**
Hybrid vaccination (BTN162b2 + Sinovac)	31 (100)	0	
Time to test			
<107 days	25 (92.6)	2 (7.4)	**0.039**
≥107 days	18 (66.7)	9 (33.3)	
Frequency of vaccination			
Two dosses	21 (38.9)	47.6	**0.000**
>Two dosses	33 (61.1)	100	

Abbreviations: CT: Chemotherapy, HT: Anti-hormone therapy, Th: therapy.

All patients who were on endocrine therapy had seropositivity. Seropositivity was higher in patients younger than 50 years of age (p=0.016). Antibody titer dynamics was significantly associated with the time to test in the patient group, patients with shorter TTT had higher titers (p= 0.039). Patients who had hybrid vaccination and patients who received >2 doses of vaccination had higher antibody titers (p=0.000, p=0.000 respectively) Presence of comorbidities, stage of disease and smoking history did not have any impact on the magnitude of antibody response.

Four patients (7.4%) in the breast cancer group (all after vaccination), and 9 (16%) participants in the control group (7 participants before vaccination and 2 participants after vaccination) had a history of COVID-19 infection.

Discussion

In this cross-sectional cohort study, we presented the level of antibody responses to SARS-CoV-2 vaccination among patients with breast cancer in comparison to healthy controls. Seropositivity rate was numerically lower in the patient group in comparison to healthy control group. It should be noted that 55.5% of patients were on chemotherapy at the time of vaccination in the patient group, potentially responsible from the attenuated immune response to vaccination. Several studies explored the immunogenicity after different types of COVID-19 vaccines in patients with cancer. All of these studies included patients with various types of solid tumors who were on different types of antineoplastic therapies. A multicenter, prospective observational study from Turkey evaluated the immunogenicity of Sinovac in 47 patients with solid tumors. Majority of the patients had cytotoxic chemotherapy, median age was 73 (64-80), none of them had previous COVID infection and serum samples were taken 4 weeks after the second dose of vaccination. SARS-COV-2 antibody was evaluated by SARS-CoV-2 total ELISA kits. Seroconversion (immunogenicity) was defined as post-vaccination positivity of SARS-COV-2 antibody (≥1 IU) that was negative (<1 IU) before vaccination. Immunogenicity rate was 63.8% in entire patient group and significantly associated with younger age (14). Another prospective, multicenter Turkish study compared the seropositivity rate of 776 cancer patients with 715 non-cancer controls after inactive CoV-2 vaccination. IgG level of >50 AU/ml was defined as seropositivity. Median age was 64 years in the patient and 50 in the control group, 39.8 % patients were on active chemotherapy, serum samples were taken 4-6 weeks from all second dose of inactive vaccine. The most common type of cancer was breast cancer (% 32). Seropositivity was lower in the patient group (p<0.001) compared to control group. Older age and chemotherapy were significantly associated with lower seropositivity (15).

A prospective observational cohort study from Hellenic Cooperative Oncology group has reported the rate of seropositivity measured 2-4 weeks after two doses of three different vaccines (BNT162b2, mRNA-1273 or AZD1222) in 189 patients with solid tumors compared to 99 healthy volunteers. Sixty-four percent of patients and 17% of healthy participants were older than 60 years of age. The seropositivity rate in patients with solid tumors was significantly lower than the control group (91% vs 98%). Forty-seven percent of the patient group were on chemotherapy at the time of vaccination.

Older age, poor performance status, active treatment, certain cancer types (pancreatic cancer, SCLC), male gender and smoking status were significantly associated with lower immunogenicity (16). A single center prospective study from Israel investigated the serologic response to COVID-19 infection and/or vaccination with BTN162b2 mRNA vaccine in 202 cancer patients and, 30 healthy controls. The median age was 62, 44% were male, 33% had breast cancer. Blood samples to analyze antibodies against spike protein were collected at a median of 77 days after the second vaccine. Fifteen % of patients had COVID infection before vaccination. Ninety-six (47.5%) patients were on chemotherapy and 19% patients were on surveillance without any therapy. Serologic response rates were 85.6% in the entire patient population, 77.5 % among patients on chemotherapy, 87.2% in patients without history of COVID infection and 100% in the control group. Chemotherapy administration was significantly correlated with lower response rate to vaccination (17). This study underscored the need for close serological surveillance and potential need for booster doses in patients with cancer. Three other studies reported >95% seropositivity rates in patients with cancer. The percentage of patients with breast cancer were in the range of 24-25%. These studies included also patients with hematological malignancies. Importantly most patients with solid tumors were on hormonal therapies and surveillance, suggesting that serologic response is higher in patients who are not on chemotherapy (18, 19, 20).

Two prospective studies from Israel reported the rate of seropositivity measured by IgG Abs against spike RBD following two doses of vaccination with BNT162b2 vaccine in the range of % 86-90. Eighteen % of patient population were patients with breast cancer in both studies and 30-58% of all patients were on CT. Chemotherapy was associated with reduced immunogenicity similar to other studies from other countries (6, 20).

Our study included a specific group of cancer patients in contrast to other reports including all types of cancers. Seropositivity was lower in breast cancer patients receiving chemotherapy +/-targeted therapy in comparison to endocrine therapy despite this difference was not statistically significant (p: 0.054). Four patients and nine participants in the control group had COVID-19 infection before blood sampling might be a potential confounder but the seropositivity rate in the control group was numerically higher than the patient group. More than half of our patients were on active chemotherapy during vaccination. This might be one of the most important reasons why seropositivity was lower in the patient group (p=0.054). Patients who were on chemotherapy were not permitted to have vaccination if they have lymphopenia (<1000) and neutropenia (<1500) at our outpatient clinics. The number of patients receiving only targeted therapy was very few to be analyzed separately. Our country's COVID-19 pandemic management policy allowed the use of two types of vaccines. Thirty-one patients (57.4%) and 48 (85.8%) healthy controls received both types of vaccination in our study. Previous studies including patients with all types of solid tumors did not have such a vaccination policy. In addition, vaccination schema was different from other countries, hybrid vaccination was most common type of vaccination schema in our study. All serological antibody measurements were performed centrally at our University Virology Laboratories. Measurement of only spike Anti-S1 RBD IgG antibody level, imbalances between the two groups in vaccination doses, presence of few patients with prior COVID infection in both cohorts and small sample size are the potential limitations of our study. Despite these limitations, our study has shown that seropositivity rate was numerically lower in patients with breast cancer compared to healthy controls in line with other studies including all types of solid tumors. Twenty percent of the patients were seronegative following at least two doses of vaccination which is little higher than reported (6-14%) in other studies (6, 19, 21). It should be noted those studies included all tumor types where the proportion of breast cancer patients was low and the seropositivity analysis based on given therapy was not reported for only breast cancer patients. In addition, the time between last vaccination and blood sampling for antibody measurement were 4-6 weeks in all other studies and it is ≥ 3months in our study. Seropositivity rate in patients and control group is in the range of seropositivity reported in other studies including all types of solid tumors and healthy controls. Chemotherapy and older age were associated with a lower antibody response following vaccination similar to other studies. Of note, hybrid vaccination and more than 2 doses of vaccination were associated with higher antibody titers both in patient and control groups.

Conclusion

Our findings point out that specific subsets of breast cancer patients might need a different vaccination strategy. Adjustments based on patient and treatment related factors might be necessary for future vaccination policies in breast cancer patients.

Declaration

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Statement of Ethics

The study was performed with the permission of the Turkish Ministry of Health and was approved by the local ethics committee (2021/13).

Informed Consent Addressed

All participants signed a written informed consent form.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contribution

Ozde Melisa Celayir, Gulcin Kahraman, Jameela Somanje, Semra Oyku Colak: collected the data. Aysun Isiklar: analyzed the data. Aysun Isiklar and Gul Basaran: wrote the study. Gul Basaran: designed the manuscript. Gul Basaran, Mustafa Serteser and Nurdan Tozun read and revised the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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