

Research Article

COVID-19 Infection After Different Combinations of Vaccines in Patients with Solid Tumors

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Abstract

Objectives: This study aimed to evaluate the cancer patients with COVID-19 infection after receiving different combinations of the COVID-19 vaccines for effective vaccination strategies.

Methods: Eighty nine point thirty three percent (89.33%) of 3832 with solid malignancy were received at least 2 doses of COVID-19 vaccine. A total of 167 cancer patients with COVID-19 infection at least 28 days after the last dose of COVID-19 vaccine were included in the study.

Results: Forty one point nine percent (41.9%) of the study population were received two doses of CoronaVac vaccine, 21.5% of the them; two doses of CoronaVac vaccine and one dose of BNT162b2 vaccine, 18.6% of them; two doses of BNT162b2 vaccine and 18% of them; three doses of CoronaVac vaccine. The median day from the last dose of vaccination to infection was significantly longer in patients with receiving cytotoxic chemotherapy than others ($p=0.02$). The requirement of oxygen support was high numerically in patients received the last of cytotoxic chemotherapy in 1-14 days prior to COVID-19 infection (23%).

Conclusion: This study outlined the similar efficacy of the different combinations of COVID-19 vaccine by evaluating the clinical parameters in patients with solid malignancy.

Keywords: BNT162b2 vaccine, COVID-19 infection, CoronaVac vaccine

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The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic has revealed to the development of vaccines based on various technologies such as BNT162b2 (Pfizer-BioNTech), CoronaVac (Sinovac Biotech), AZD1222 (Oxford/AstraZeneca), mRNA-1273 (Moderna), Ad26.COV2.S (Johnson & Johnson), Sputnik V (Gamaleya), as SARS-CoV-2 infection is associated with significant mortality and morbidity. BNT162b2, a nucleoside-modified mRNA vaccine and CoronaVac inactivated SARS-CoV-2 vaccine are the mostly used vaccines in Turkey.^[1,2]

The patients with cancer are more vulnerable to serious Coronavirus Disease 2019-related (COVID-19) complica-

tions and mortality due to factors such as advanced age, comorbidities, immunosuppression, poor health status, so that vaccination against COVID-19 has been widely encouraged in patients with cancer, regardless of the origin of disease, the type of treatment.^[3,4]

The efficacy and optimal timing of vaccination in relation to cycles of chemotherapy for an effective immunity in this patient spectrum remains an important focus of the studies which do not provide satisfactory information unlike in general population. Studies using anti-SARS-CoV-2 spike protein immunoglobulin G titres, demonstrated an insufficient response after vaccination in patients with cancer. Becerril-

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Gaitan et al showed in their metaanalysis that patients with cancer have a lower immune response after COVID-19 immunization than with non-cancer patients.^[5] Furthermore, in the the studies it is demonstrated that having haematological malignancies, receiving oncologic regimens like monoclonal antibodies (anti-CD20, anti-CD38), have been associated with lower immunological responses.^[6-8]

Addeo et al. demonstrated that after vaccination with second dose of mRNA vaccine, antibody titers were higher than in patients with solid cancers than in those with haematological malignancy. Although endocrine therapy or immunotherapy (immune checkpoint inhibitors) did not have effect the seropositivity rates, anti-CD20 therapy lowered the immunological responses. Also, lower rates of seropositivity were in seen in patients with partial vaccination than fully vaccination.^[8] In the multicenter study, Karacin et al showed that immunogenicity rate of the CoronaVac vaccine was 59.5% in the cancer patients receiving at least one cytotoxic therapy consisted with other studies.^[9] While Massarweh et al demonstrated 90% seropositivity in cancer patients received BNT162b2 mRNA vaccine, Ariamanesh et al showed 86.9% seropositivity in cancer patients received inactivated vaccine.^[3,10]

The current study aimed to evaluate the frequency of COVID-19 infection after vaccination in cancer patients with different combinations of the vaccines. Secondary hypothesis of the study was to compare the effect of different vaccination combinations on COVID-19 infection clinic in cancer patients after vaccination.

Methods

Three-thousand, eight hundred and thirty-two patients, admitted to our oncology clinic between July 2021 and December 2021 with the diagnosis of solid malignancy were evaluated. Most of these patients were (89.33%) received at least 2 doses of COVID-19 vaccine. The patients with COVID-19 infection in the first 28 days after after COVID-19 vaccination and the patients with inadequate data were not included in the study. Also, the patients with one dose of COVID-19 vaccine were excluded from the study. So, a total of 167 patients with COVID-19 infection at least 28 days after the last dose of COVID-19 vaccine were included in the study population.

Sociodemographic and clinical characteristics of the patients, types of vaccines administered and laboratory data obtained at the time of the COVID-19 infection were recorded from the hospital data system. The patients were categorized into four groups according to the different combinations of vaccines administrated as patients received two doses of CoronaVac vaccine, three doses of

CoronaVac vaccine, two doses of CoronaVac and one dose of BNT162b2 vaccine and also two doses of BNT162b2 vaccine. Furthermore, the patients received with at least one dose of BNT162b2 vaccine and without BNT162b2 vaccine was compared according to sociodemographic and clinical characteristics and also laboratory parameters.

Statistical Analysis

Statistical analysis was performed with the statistical package (SPSS 23). The variables were examined with visual and analytical methods to determine for normal distribution. Descriptive analyses were presented using medians for non-normally distributed and ordinal variables. The Chi-square or Fisher's exact test was used to compare gender, receiving respiratory support, requirement of intensive care unit management and mortality. Non-parametric tests were used to compare the non-normally distributed variables. The possible factors stated with univariate analyses were evaluated using logistic regression analysis to determine independent predictors. A p-value of less than 0.05 was accepted to be statistically significant.

Results

Eighty nine point thirty three percent (89.33%) of 3832 cancer patients, followed in oncology clinic between July 2021 and December 2021 received at least two doses of vaccine; 22.02% received two doses of BNT162b2 vaccine, 14.92% received three doses of CoronaVac vaccine, 10.22% received two doses of CoronaVac vaccine, 35.77% received two doses of CoronaVac and one dose BNT162b2 vaccine. While 17.86% of the patients received two doses of CoronaVac vaccine were infected with COVID-19, 5.2% of the patients received three doses of CoronaVac vaccine were infected with COVID-19. Also, it is reported that 3.67% of the patients received two doses of BNT162b2 vaccine and 2.62% of the patients received two doses of CoronaVac and one dose BNT162b2 vaccine were infected with COVID-19. There was no statistically quantitative significance between vaccination groups and the rate of being infected with COVID-19 ($p=0.36$).

The median age of total 167 cancer patients with COVID-19 infection at least 28 days after the last dose of COVID-19 vaccine was 63 (25-83) years. Most of them were male (51.5%). Hypertension, diabetes mellitus, coronary heart disease and chronic obstructive pulmonary disease (COPD) were the most common comorbidities seen in the patients. The gastrointestinal, lung, breast and genitourinary tumors were among the common diagnoses of the patients. The rate of the patients were not receiving any anti-cancer therapy within 1 months before COVID-19 infection was 33.5%. The cytotoxic chemotherapy was the most common anti-cancer

therapy received in the study population (48.5%) and was followed by hormonotherapy (10.5%), targeted therapy (6.6%) and immunotherapy (0.6%). When we examined the patients according to their vaccination status, it was seen that 41.9% of the cases were received two doses of CoronaVac vaccine, 21.5% of the them two doses of CoronaVac vaccine and one dose of BNT162b2 vaccine, 18.6% of them BNT162b2 vaccine and 18% of them three doses of CoronaVac vaccine. The basic demographic and clinical characteristics of the patients were shown in the Table 1.

Table 1. Basic demographic and clinical characteristics of the study population

Parameters	Results
Median age (years)	63 (25-83)
Male (n-%)	86 (51.5)
Comorbiditidy (n-%)	
Hypertension	55 (32.9)
Diabetes mellitus	46 (27.5)
Coronary heart disease	24 (14.4)
Chronic obstructive pulmonary disease	18 (10.8)
Primary malignancy (n-%)	
Gastrointestinal	42 (25.1)
Lung	37 (22.2)
Breast	32 (19.2)
Genitourinary	28 (16.8)
Others	19 (11.3)
Head and neck cancer	9 (5.4)
Type of anti-cancer treatment within 1 months before COVID-19 infection (n-%)	
Cytotoxic chemotherapy	81 (48.5)
Hormonotherapy	18 (10.8)
Targeted therapy	11 (6.6)
Immunotherapy	1 (0.6)
No treatment	56 (33.5)
Vaccination status of the patients (n-%)	
Two doses of CoronaVac vaccine	70 (41.9)
Two doses of CoronaVac vaccine and one dose of BNT162b2 vaccine	36 (21.5)
Two doses of BNT162b2 vaccine	31 (18.6)
Three doses of CoronaVac vaccine	30 (18)
Median day from the last dose of vaccination to COVID-19 infection	94 (28-268)
Hospitalization status (n-%)	
Outpatient clinic management	112 (67)
Inpatient clinic management	34 (20.4)
Intensive care unit management	21 (12.6)
Receiving respiratory support (n-%)	40 (24)
Median time of hospital stay (day)	10 (3-75)
Mortality (n-%)	11 (6.6)

COVID-19: Coronavirus Disease 2019.

The median day from the last dose of vaccination to COVID-19 infection was found to be 94 (28-268) days in the study. After detailed examination, 67% of the patients were treated at outpatient clinic. As 20.4% of the patients were treated at inpatient clinic, 12.6% of the patients were followed up at the intensive care unit with median of hospital stay was 10 (3-75) days. During the follow up, 6.6% of the patients were died. Most of the died patients had (81.8%) metastatic disease. The most common diagnosed solid malignancy in these patients were colon cancer (27.3%). When we evaluated independent predictors of mortality, it was seen that being diagnosed with COPD were associated with the greater the probability of death (OR = 1.48; 95% CI 1.23- 1.69). But, there was no significant relationship between age, gender, vaccine type, comorbidities other than COPD with COVID-19-related death. Furthermore, there was no significant relationship between the possible factors such as comorbidities, age, gender and staying in intensive care unit or inpatient clinic.

When the patients were compared according to the different types of vaccination status, patients received two doses of BNT162b2 vaccine were younger than other patient groups which was statistically significant ($p=0.001$) (Table 2). There was no significant differences in the gender, median time of hospital stay, inpatient clinic and intensive care unit stay, receiving respiratory support and intensive care unit management, mortality between the patient groups (Table 2). When C-reactive protein ($p=0.27$), white blood cell ($p=0.31$), fibrinogen ($p=0.54$), D-dimer ($p=0.82$) values were between the groups at the time of infection no significant difference was found.

It was also shown that the patients received at least one dose of BNT162b2 vaccine was younger than other patients ($p=0.002$). Although the clinical parameters of the patients were not different between the patients, procalcitonin levels of the patients with at least one dose BNT162b2 vaccine was lower than other patients which was statistically insignificant (respectively; 0.11 (0.02-2.59), 0.26 (0.02-63,64), $p=0.08$).

Patients receiving active chemotherapy during COVID-19 infection after vaccination were more advanced aged ($p=0.07$). Also, there was a female dominance in patients with not receiving cytotoxic chemotherapy ($p=0.01$) (Table 3). The median time of hospital, inpatient clinic and intensive care unit stay was similar in patients who were receiving and not receiving cytotoxic chemotherapy (respectively; $p=0.22$, 0.06 and 0.47). Also, it was seen that the median day from the last dose of vaccination to infection was significantly longer in patients with receiving cytotoxic chemotherapy than others ($p=0.02$) (Table 3). It was also analysed that patients received cytotoxic chemotherapy was received higher rate of at least one dose of BNT162b2

Table 2. Comparison of the some demographic and clinical parameters related with the treatment of the COVID-19 infection according to vaccination status of the patients

Parameter	Two doses of CoronaVac vaccine (n=70)	Two doses of CoronaVac and one dose of BNT162b2 vaccine (n=36)	Two doses of BNT162b2 vaccine (n=31)	Three doses of CoronaVac vaccine (n=30)	p
Median age (years)	65 (29-82)	67 (25-83)	52 (34-72)	65.5 (33-74)	0.001
Female (n-%)	36 (51.4)	15 (41.7)	14 (45.2)	16 (53.3)	0.30
Median time of hospital stay (day)	10 (3-75)	10.5 (4-30)	9 (6-37)	15.5 (7-42)	0.37
Median time of inpatient clinic stay (day)	9 (3-30)	8.5 (3-24)	9 (2-35)	14 (2-24)	0.31
Median time of intensive care unit stay (day)	7 (2-47)	6.5 (3-8)	4 (2-7)	5 (3-18)	0.76
Median day from the last dose of vaccination to infection	96.5 (28-268)	86.5 (28-189)	118 (28-189)	88.5 (28-197)	0.46
Receiving respiratory support (n-%)	17 (24.3)	10 (27.8)	6 (19.4)	7 (23.3)	0.86
Requirement of intensive care unit management (n-%)	10 (14.3)	4 (11.1)	3 (9.7)	4 (13.3)	0.52
Mortality (n-%)	5 (7.1)	2 (5.6)	3 (9.7)	1 (3.3)	0.96

Table 3. Comparison of the patients according to receiving cytotoxic chemotherapy before COVID-19 infection

Parameter	Patients receiving cytotoxic chemotherapy (n=81)	Patients not receiving cytotoxic chemotherapy (n=86)	p
Median age (years)	65 (34-83)	60.5 (25-80)	0.07
Female (n- %)	31 (38.3)	50 (58.1)	0.01
Median time of hospital stay (day)	9 (3-75)	12 (4-42)	0.22
Median time of inpatient clinic stay (day)	8 (2-30)	10 (3-35)	0.06
Median time of intensive care unit stay (day)	6.5 (2-47)	7 (2-18)	0.47
Median day from the last dose of vaccination to infection	118 (28-229)	90 (28-268)	0.02
Receiving respiratory support (n-%)	17 (21)	23 (26.7)	0.38
Requirement of intensive care unit management (n-%)	10 (12.3)	11 (12.8)	0.97
Mortality (n-%)	7 (8.6)	4 (4.7)	0.30

vaccine than patients not received (42%, 38.4%, $p=0.37$).

When the median time between the last dose of cytotoxic chemotherapy and COVID-19 infection was stratified as 0-15 days, 15-28 days and >28 days, there was no significant difference between these groups in means of median hospital, in inpatient clinic and intensive care unit stay and also in means of median day from the last dose of vaccination to infection (respectively; $p=0.92$, 0.72, 0.19, 0.63). Requirement of oxygen support in patients received the last dose of cytotoxic chemotherapy in 1-14 days prior to COVID-19 infection was 23% compared with patients received in 15-28 days (18.2%) and patients received in >28 days (19%)($p=0.63$). Furthermore, mortality rate was higher in patients received the last dose of cytotoxic chemotherapy in 1-14 days prior to COVID-19 infection (10.5%) than other patients (9.1%, 4.8%)($p=0.46$).

Discussion

The current study demonstrated that the rate of at least 2 doses of vaccination was high in cancer patients and after 2 doses of CoronaVac vaccine, high rate of (17.86%) COVID-19 infections was encountered. Although this high rate was not statistically significant, it might have clinical significance. The rate of COVID-19 infection was low in other vaccine groups. Among the vaccine groups; it was shown that there was no difference in terms of hospitalization, inpatient and intensive care unit follow-up and laboratory parameters. It was also seen that all patients were infected within 94 days (28-268) after the last dose of vaccine. We found that the time from the last dose of vaccine to COVID-19 infection was significantly longer in patients receiving cytotoxic therapy ($p=0.02$). Also, 12.6% of the patients

required intensive care support during the follow-up, and that 6.6% of the patients died after vaccination. This study demonstrated one of the first preliminary clinical outcomes of COVID-19 infection after full dose vaccination in solid cancer patients.

The Coronavirus Disease 2019 pandemic has effected both social and economic life all over the world. As the pandemic has resulted in mortality and morbidity especially in high risk patients like advanced aged, immunocompromised patients, Turkey's national vaccination protocol have carried out prioritizing to receive vaccine in these patient population. There are a lot of different combinations of vaccines used all around the world.^[11] In Turkey, the mostly used protocol of vaccination comprise BNT162b2, CoronaVac and its different combinations. In our oncology clinic, when we analysed the cancer patients, it was shown that 89.33% of them received at least two dose of vaccine in different combinations. The rate of vaccination status in this study was higher compared to vaccination status of Turkish population (%85,67) according data of Turkish Ministry of Health.^[12] To the best of our knowledge the current study is the one of first which analyzes the patients infected with COVID-19 after receiving different combinations of the vaccines.

The studies demonstrated that the cancer patients have a higher need of intensive care unit stay and higher mortality and morbidity, so that the efficacy of COVID-19 vaccine in cancer patients is important.^[4] The timing, type of the vaccine and also frequency of the vaccine in relation to the cycles of chemotherapy are the mainstays of the most studies. It was seen that there was no any significant difference between vaccination with different types of vaccines and the rate of being infected with COVID-19. Remarkably, the patients received two doses CoronaVac vaccines were infected with numerically higher rate than other patients (%17,86). However the numerical difference did not achieve statistically meaningful difference. The high incidence of COVID-19 infection after 2 doses of CoronaVac vaccine may have clinical significance and we can say that 2 doses of inactivated vaccine are less effective.

In the studies, the efficacy of COVID-19 vaccines was evaluated by measuring the post vaccine antibody titers to the viral spike protein, but in our study we analyzed the important clinical parameters of the COVID-19 infection as a marker of the efficacy.^[3, 13-15] Our study demonstrated that there were no significant differences in the gender, median time of hospital stay, duration of inpatient clinic and intensive care unit stay, rate of patients receiving respiratory support and needs intensive care unit management, mortality between the patient groups. Furthermore, difference was not found in the laboratory parameters between the

patients according to vaccination status.

There is no consensus on the type and number of the vaccine applied in the cancer patients. In our study, although the clinical parameters of the patients such as median time of hospital, inpatient clinic and intensive care unit stay were not differ between the patients, procalcitonine levels of the patients with at least one dose BNT162b2 vaccine were lower than other patients which was statistically insignificant ($p=0.08$). But in our study, it was emphasized that the patients received at least one dose of BNT162b2 vaccine were younger than other patients ($p=0.002$). It can be interpreted as younger cancer patients may have preferred the BNT162b2 vaccine more frequently because there are more studies on the efficacy and safety of BNT162b2 vaccine and more scientific data regarding its superiority over CoronaVac.^[3,8]

During the pandemic, the cancer patients have had trouble in receiving active cancer treatment. As the pandemic has progressed, it has revealed that increased mortality in cancer patients with COVID-19 infection is mainly associated with older age and comorbidities. The studies did not demonstrate significant association between mortality and receiving cytotoxic chemotherapy or non-cytotoxic treatment.^[16] It should be outlined that the patients receiving cytotoxic chemotherapy monitored routinely by laboratory studies and imaging studies during pandemic due to status of immunosuppression. In our study, we found that the length of median stay at inpatient clinic was longer in patients who did not receive cytotoxic chemotherapy. Also, it was seen that the median day from the last dose of vaccination to infection was significantly longer in patients with receiving cytotoxic chemotherapy than others ($p=0.02$). This might be related that after the data published that patients receiving chemotherapy had higher mortality according to COVID-19 infection, the oncologist might be more alert compared to previous years of COVID-19 pandemic. Also, the patients with receiving cytotoxic chemotherapy might isolated themselves from the community due to fear of infection. Therefore, the COVID-19 infected patients who received chemotherapy were hospitalized for closer follow up under vision of oncologist due to fear of mortality and morbidity related with COVID-19 infection. ($p=0.06$). This finding may have resulted from the different approaches of medical centers which followed up immunosuppressed patients. Also, it was seen that patients received cytotoxic chemotherapy was received higher rate of at least one dose of BNT162b2 vaccine than patients not received. In our study, as we found that patient with at least one dose of BNT162b2 was lower procalcitonin levels, we interpreted this finding that BNT162b2 vaccine could be protective from infection with more severe clinic.

While some studies recommends vaccination at least two weeks before starting chemotherapy, some recommends whenever available.^[17,18] The vaccines are suggested when leucopenia or pancytopenia has resolved.^[18] In our study, the findings were consistent with the literature; it was found that requirement of oxygen support was numerically higher in patients received the last of cytotoxic chemotherapy in 1-14 days prior to COVID-19 infection than patients received in 15-28 days and in >28 days ($p=0.63$). Furthermore, mortality rate was higher in patients received the last of cytotoxic chemotherapy in 1-14 days prior to COVID-19 infection (10.5%) than other patients ($p=0.46$).

Finally the rate of following up in intensive care unit after COVID-19 infection was high patients with malignancy in the studies.^[19] While Zhang et al. showed this rate as 21.6%, Yang et al. found this rate as 20%.^[20,21] In our study, we found that the rate of intensive care unit management of patients with after COVID-19 vaccine was %12.6 and this finding demonstrated that COVID-19 vaccination could reduce the need of intensive care unit management. Another important issue that the mortality rate was reported as high as 28.6% in cancer patients in Chinese study.^[20] Giannakoulis et al. found an increased mortality in patients with cancer 13.5%.^[4] In our study, we found mortality rate lower (6.6%), which support the idea that the COVID-19 vaccination reduce the mortality rate in patients with solid malignancy.

Our study has some limitations. Firstly, our study population with median age of 63 years was old aged so the immunogenicity to COVID-19 vaccines can be lower. Secondly, number of the patients was limited. Furthermore, due to retrospective design of the study, we could not get some data such as using corticosteroids which can affect the response to COVID-19 vaccine. The primary malignancies, history of cancer treatment of the patients (types, lines of therapy), stage of the disease were different so that our population was heterogenous. This might effect the results.

Conclusion

Our study showed one of the first preliminary clinical outcomes of COVID-19 infection after full dose vaccination in solid cancer patients. This study showed that, there were no statistically significant difference between clinical parameters of cancer patients diagnosed as COVID-19 after at least two dose vaccination. Interestingly, it was seen demonstrated that time from the last dose of vaccine to COVID-19 infection was significantly longer in patients receiving cytotoxic therapy which may related to social iso-

lation of this patient group, close follow-up of the physicians. Considering the fluctuating course of the pandemic, prospective studies should be conducted on the efficacy of different combinations of vaccines for higher immunogenicity and reduction of mortality and morbidity risk due to COVID-19 infection in the cancer population in patients with solid malignancies.

Disclosures

Ethics Committee Approval: The study protocol was approved by the ethics committee of Gazi University Faculty of Medicine (2022-189).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – O.Y.; Design – O.Y., O.U.; Supervision – A.O., N.O.; Materials – O.Y., N.O., G.S., A.O.; Data collection &/or processing – O.U., O.Y., N.O.; Analysis and/or interpretation – O.U., O.Y.; Literature search – O.U., G.S., O.Y.; Writing – O.U., O.Y.; Critical review – O.Y., G.S., N.O., A.O.

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