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Effect of tyrosine kinase inhibitor and conventional chemotherapy on COVID-19 antibody level in hematological patients

Ahmet Kaya[1], İlhami Berber[1], İrfan Kuku[1], Mehmet Ali Erkurt[1], Emin Kaya[1], Soykan Biçim[1], Emine Hidayet[1], Salih Cırık[1], Süleyman Arslan[1], Fatma Hilal Yağın[2], Ahmet Sarıcı[1]

[1]*Division of Hematology, Department of Internal Medicine, Faculty of Medicine,, Turgut Özal Medical Center, İnönü University, Malatya, Turkey*
[2]*Department of Biostatistics and Medical Informatics, Faculty of Medicine, İnönü University, Malatya, Turkey*

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Corresponding Author: İlhami Berber, ilhami.berber@inonu.edu.tr

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ABSTRACT

Aims: In this study, we aim to discover if there is a difference between COVID-19 antibody level in hematological patients taking conventional chemotherapy and tyrosin kinase inhibitors.

Methods: COVID-19 IgG levels were measured using the QuantiCOR anti-SARS-CoV-2 IgG ELISA test kit on 74 patients who received chemotherapy and used tyrosine kinase inhibitors in the adult hematology clinic of Turgut Özal Medical Center between May 2019 and January 2022. Age, height, weight, badimeks index of the patients were measured, the doses and durations of vaccine use, the time between the first vaccine and the second vaccine, how long after the first vaccine antibodies were checked, and vaccine-related side effects were recorded. Collected data statistical analysis was performed using Python 3.9 and IBM SPSS Statistics for Windows version 26.0 (New York; USA).

Results: Antibody levels of the patients were significantly higher in the healthy control group than in the groups that received chemotherapy and tyrosine kinase inhibitors. Antibody levels of female patients in the control group were higher than male patients. Antibody levels of the patient groups receiving chemotherapy and tyrosine kinase inhibitor were not found to differ between the two groups. When the patients receiving B lymphocyte suppressing chemotherapy in the chemotherapy group were compared with the control group, antibody levels were found to be higher in the control group.

Conclusion: COVID-19 vaccination in hematological cancers did not produce adequate antibody response, especially in patients receiving chemotherapy or tyrosine kinase inhibitors.

Keywords: COVID-19 vaccine, tyrosine kinase inhibitor, chemotherapy, anti-SARS-CoV-2 IgG

INTRODUCTION

In February 2020, the World Health Organization designated the virus that caused the epidemic as the disease COVID-19.[1] During the pandemic providing medical care for patients with cancer or suspected cancer, managing the risks of death from cancer against serious complications arising from it has been very difficult given the possible higher lethality of COVID-19 in immunocompromised cancer patients.[2] In order to control the current pandemic, vaccination studies have been started in many centers.

Surface spike protein is the antigenic target for COVID-19 vaccines. Binds to host cells and induces membrane fusion.[3-7] It is recommended that all individuals with cancer be uptodate on their vaccination to prevent COVID-19 Infection. Patients with cancer may have attenuated response to vaccines, but vaccination is recommended in populations with cancer.[8] In patients with cancer, the COVID-19 vaccine reduces the risk of infection and can be administered safely.[9-11] However, studies also show that vaccine efficacy is reduced in those with active cancer compared to those without cancer, particularly those with hematological malignancies, and those receiving anti-CD20 antibody therapy in particular.[12] Immunogenicity studies also show reduced immune response in cancer patients, particularly those with hematological malignancies.[12] Cancer patients receiving immunosuppressive therapy should receive the third dose at least 28 days later. The third dose has been shown to be effective against the Omicron variety in cancer patients receiving treatment, but the response is poor in hematological cancers.[13,14] Current data support booster vaccination in cancer patients receiving immunosuppressive therapy.[15] The most current approach is to vaccinate between treatment regimens.[16-18]

The aim of this study is to examine the effects of the use of tyrosine kinase inhibitor (TKI) and conventional chemotherapy (CT) on the levels of COVID-19 antibodies in patients diagnosed with hematological cancer.

METHODS

COVID-19 IgG levels were measured using the QuantiCOR anti-SARS-CoV-2 IgG ELISA test kit on 74 patients who received chemotherapy and used TKIs in the adult hematology clinic of Turgut Özal Medical Center between May 2019 and January 2022. Age, height, weight, body mass index (BMI) of the patients were measured, the doses and durations of vaccine use, the time between the first vaccine and the second vaccine, how long after the first vaccine antibodies were checked, and vaccine-related side effects were recorded. Collected data Statistical analysis was performed using Python 3.9 and IBM SPSS statistics for Windows version 26.0 (New York; USA). This study was approved by Inönü University Clinical Research Ethics Committee 2021/151 protocol code. All ethical procedures and standards were carried out in accordance with the 1975 Helsinki Declaration.

Antibody Determination

Specific IgG antibodies against SARS-CoV-2 were measured in human sera by a commercial enzyme-linked immunosorbent assay (QuantiCOR anti-SARS-CoV-2 IgG ELISA test kit, Y Immunotek A.Ş., Malatya, Türkiye). This test kit was independently tested and approved by the Ministry of Health of Türkiye, General Directorate of Public Health, Department of Microbiology Reference Laboratories and Biological Products (MRLBP) by applying the World Health Organization (WHO) criteria. MRLBP is the single official authority for the endorsement of all Covid-19 test materials before commercialization. Data was presented as relative unit per milliliters (RU/mL) and the cut-off value for positive sera was 10 RU/mL.

Statistical Analysis

Qualitative data were summarized by number and percentage, and quantitative data by median and interquartile range. The Kruskal-Wallis test was used to examine the difference between groups. Since the multivariate analysis assumptions could not be provided (Multivariate normal distribution and homogeneity of variances assumptions) for the antibody level, two-way PERMANOVA (Permutational Analysis of Variance) analysis was performed using the Bray-Curtis distance (Permutation N=9999) as the similarity matrix to examine the difference between the groups and the interaction effect. $p<0.05$ was considered significant. Analyzes were performed using Python 3.9 and IBM SPSS Statistics for Windows version 26.0

RESULTS

Data of 74 patients, 27 (36.5%) female and 47 (63.5%) male, were used in the study. Descriptive statistics data regarding the demographic information of the patients are presented in Table 1. There was a significant difference between the groups in terms of antibody level. Antibody levels of the patients were significantly higher in the control group than in the patient groups receiving CT and TKI in Table 2. In the research data, a statistically significant difference was found in terms of antibody levels in male and female healthy control groups (p1=0.04). There was a statistically significant difference between the patient groups (TKI-CT-Control) in terms of antibody levels (p2<0.001). While there was a statistically significant difference in antibody level between TKI-Control (p3=0.001) and CT-Control (p3<0.001) groups, there was no statistically significant difference between TKI and CT (p3=0.12) groups. According to the data obtained in the study, the interaction effect (Gender * Group) was statistically significant (p=0.035). As a result, in addition to affecting the antibody levels of the patients separately according to gender and groups, the gender-group interaction was found to be statistically significant especially for the antibody level.

Table 1. Descriptive statistics

Variable **	Group *			p value
	CT	TKI	Control	
Age	70[a] (18)	53[b] (20.25)	35c (8.5)	<0.001
Height (cm)	170[a] (17.5)	170[a] (8.5)	168[a] (11.5)	0.66
Weight (kg)	76[a] (16)	81[a] (14.5)	73[a] (24.5)	0.11
BMI (kg/m2)	26.28[a] (5.685)	28.415[a] (3.55)	26[a] (4.4)	0.13

*: There is a statistically significant difference in group categories that do not contain the same letter. **: Variables are summarized as 'median (interquartile range)'. BMI: body mass index

Table 2. Group comparison results

Variable**	Group*			p value
	CT	TKI	Control	
Antibody level	1.67[a] (10.405)	7.105[a] (14.588)	54[b] (150.75)	<0.001
How many days between the first vaccination and the 2nd	28[a] (0)	28[a] (3)	28[a] (0)	0.98
How many days after the 2nd vaccine, antibodies were tested	90[a] (60)	90[a] (15)	172.5[a] (356.25)	0.44

*: There is a statistically significant difference in group categories that do not contain the same letter. **: Variables are summarized as 'median (interquartile range)'.

The antibody levels of the female patients in the control group were found to be higher than the antibody levels. male patients and other groups of the study (Table 3). The antibody level in the control group was statistically significantly superior than in the patient group receiving R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) - R-BENDA (rituximab, bendamustine) chemotherapy. There was no statistical difference when the patient group receiving R-CHOP - R-BENDA conventional chemotherapy was compared among themselves. (Table 4). Post vaccination joint pain in 4 patients, skin allergy in 1 patient, dizziness in 1 patient, tachycardia in 1 patient were observed as vaccine-related side effects (Table 5).

Table 3. Two-way PERMANOVA results for antibody level

Groups	Median (IQR)	Sex Main Effect	Group Main Effect	Interaction
		p1 Value	p2 Value	
Antibody level-TKI-Female	26.4 (48.55)	p1=0.04	p2<0.001 TKI-CT p3=0.12 TKI-Control p3=0.001 CT-Control p3<0.001	p=0.035
Antibody level-TKI-Male	4.42 (10.78)			
Antibody level-CT-Female	1.67 (13.55)			
Antibody level-CT-Male	1.48 (7.48)			
Antibody level-Control-Female	78 (184.62)			
Antibody level-Control-Male	53.3 (142)			

CT: chemotherapy, TKI: tyrosine kinase inhibitor. IQR: interquartile range, p1 Value; significance test result between women and men, p2 value; intergroup PERMANOVA significance test result, p3: the results of the in-group comparison significance test., Interaction: Sex * Group

Table 4. Comparison results between control, R-chop and R-benda

	Group		p value
	R-CHOP and R-BENDA	CONTROL	
	Median (IQR)	Median (IQR)	
Antibody level	1 (2.64)	54 (162.4)	<0.001
Number of days between the first and the second vaccine	28 (0)	28 (0)	0.62
How many days after 2nd vaccine, antibody tested	90 (60)	165 (360)	0.42

IQR: interquartile range, R-CHOP; Rituksimab-siklofosfamid-doksorubisin-vinkristin-prednizon, R-BENDA; Bendamustine +Rituximab

Table 5. Descriptive statistics of patients related to Covid-19 and vaccine for groups

Variable	Category	Group		
		CT	TKI	Control
		n (%)	n (%)	n (%)
Has he/she had Covid-19 illness?				
	No	21 (77.78)	22 (91.67)	6 (26.09)
	Yes	6 (22.22)	2 (8.33)	17 (73.91)
Vaccine				
	2 doses of sinovac	12 (60.00)	24 (100.00)	6 (27.27)
	2 doses of biontech	2 (10.00)	0 (0.00)	2 (9.09)
	3 doses of sinovac	2 (10.00)	0 (0.00)	1 (4.55)
	3 doses of sinovac + 1 dose of biontech	1 (5.00)	0 (0.00)	1 (4.55)
	2 doses of sinovac + 1 biontech	1 (5.00)	0 (0.00)	5 (22.73)
	2 doses of sinovac + 2 biontech	2 (10.00)	0 (0.00)	5 (22.73)
	3 doses of biontech	0 (0.00)	0 (0.00)	2 (9.09)
Post-vaccine side effect?				
	No	24 (88.89)	21 (87.50)	16 (69.57)
	Yes	3 (11.11)	3 (12.50)	7 (30.43)

Table 6. Chemotherapy received by patients receiving chemotherapy (CT)

Variable	n (%)
Brentiksumab	2 (7.4)
Desitabine	1 (3.7)
DRC	1 (3.7)
DRD	1 (3.7)
Ixazomibe + Lenalidomide	1 (3.7)
Mini CHOP	1 (3.7)
R-BENDA	4 (14.81)
R-CHOP	6 (22.22)
Lenalidomide	6 (22.21)
VCD	2 (7.4)
Azasitidine	2 (7.4)

DRC; Cyclophosphamide - Dexamethasone – Rituximab, DRD; Daratumumab, lenalidomide, and dexamethasone , R-CHOP; Rituksimab-siklofosfamid-doksorubisin-vinkristin-prednizon, R-BENDA; Bendamustine +Rituximab, VCD; cyclophosphamide+ bortezomib+ dexamethasone

Table 7. Tyrosine kinase inhibitors used by patients (TKI)

Variable	n (%)
Bosutinib	2 (8.32)
Dasatinib	4 (16.67)
Imatinib	14 (58.33)
Nilotinib	4 (16.67)

DISCUSSION

During the pandemic, viral antibody level has an important place in isolating the population. There are many questions clinicians need to answer regarding COVID-19 diagnostic testing.[19] Since COVID-19 is fatal in cancer patients, prophylaxis for the disease is needed. In the study of Thakkar A et al.[20] a high antibody response rate (94%) was observed in 200 patients treated for cancer in New York and immunized with vaccines that act on COVID-19 surface protein. Solid tumors (98%), patients with hematological cancer (85%), especially patients who received CD 20 monoclonal antibodies with high immunosuppressive properties, had a lower rate of antibody responses (70, 73%). High antibody response was seen after vaccination in patients receiving immune checkpoint inhibitors (97%) or patients receiving hormonal therapy.

Patients with COVID-19 infection had higher seroconversion titers after vaccination. Relatively lower IgG titers were seen after vaccination with vaccines developed against the surface protein than with mRNA based vaccines.[20] In this study, hematological malignancies were compared and the antibody level of the patients who received TKI and CT was found to be lower than the control group. This decrease was found to be statistically significant. However, in the study, no significant difference was found between the patients who received TKI and those who received CT in terms of antibody levels. (CT-Control p3<0.001, TKI-Control p3<0.001, TKI-CT p3<0.12). In particular, female patients in the Control group had higher antibody levels compared to male patients and other groups of the study (p1<0.04). In the study of Ollila TA et al.[21] 160 patients with cancer were examined for response to COVID-19 vaccines. In the study, 105 (66%) patients received B-cell-reducing monoclonal antibodies, most commonly.

Patients with active disease have a higher antibody response than patients in remission or waiting without any cancer treatment. The time from the last chemotherapy administration to vaccination was associated with increased antibody response rates. While 69% of patients who completed their chemotherapy more than 12 months ago had an antibody response, this rate was found to be 24% in those who were vaccinated within 12 months. It has been observed that the antibody response to the COVID-19 vaccine is lower in patients using B cell destroying antibodies.[21] In the study, ten patients who received CT used B cell reducing monoclonal antibody. When the patient group receiving R-CHOP - R-BENDA conventional chemotherapy was compared among themselves, no statistical difference was observed, but when compared with the control group, the antibody level was found to be significantly higher in the control group. In the study of Mair MJ et al.[12] after the first vaccination, anti-S antibody levels were found to be lower in patients with hematological cancer who received B cell targeting agents than those who received other treatments. After the first vaccination, anti S levels were found to differ according to the ongoing antineoplastic treatment modalities. Antibody levels after full immunization have been found to be higher in healthcare workers than in patients with cancer or in patients continuing treatment in combination with immunotherapy. In the study, the antibody response of the patients who received TKI and conventional chemotherapy was found to be statistically significantly lower than the healthy control group. (CT-Control p3<0.001, TKI-Control p3<0.001, TKI-CT p3<0.12).

CONCLUSION

COVID-19 vaccination in hematological cancers does not produce adequate antibody response, especially in patients receiving CT or TKIs. However, vaccination is recommended in immunocompromised patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Malatya Clinical Researches Ethics Committee (Decision No: 2021/151).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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