DOI: 10.4149/BLL_2023_030

Bratisl Med J 2023; 124 (3)

187 – 192

CLINICAL STUDY

COVID-19 vaccine immunity in oncology patients

Gonca Hanedan USLU[1], Sema Yilmaz RAKICI[1], Aysegul Copur CICEK[2], Zihni Acar YAZICI[3]

Recep Tayyip Erdogan University Faculty of Medicine, Rize, Turkey. **gonca.uslu@erdogan.edu.tr**

ABSTRACT

BACKGROUND: To investigate the effect of vaccine types applied in our country against 2019 coronavirus disease on the formation of protective antibodies in oncology patients.

MATERIALS AND METHODS: The data of 81 cancer patients who received at least one dose of vaccine for COVID-19 and radiotherapy were analyzed retrospectively. At any time after the vaccination, blood samples were taken and the antibody titers against the vaccine were measured.

RESULTS: There were 28 (34.6 %) patients who received two doses of vaccine and 48 patients (59.3 %) who received 3 doses of vaccine (Sinovac only), while 26 patients (32.1 %) were given both vaccines. The mean time for antibody measurement was 62 days after the last vaccination. IgG levels were significantly higher in patients who received Biontech vaccine than in those who received Sinovac ($r = 0.525$; $p < 0.001$). While chemotherapy was the factor that decreased the mean IgM level ($p = 0.044$), advanced disease (stages 3 and 4) was a significant factor that increased the mean IgG level ($p = 0.047$). A statistically significant negative correlation was found between IgM antibody level and WBC count after first vaccination ($r = –0.251$; $p = 0.024$). For every WBC count unit increase in the first vaccination period, there was a 1.333-fold increase in the risk of IgM negativity.

CONCLUSION: The Biontech vaccine produced higher antibody levels in advanced oncology patients. While the application of radiotherapy in cancer patients was not found to be an effective factor in the vaccination status, it was determined that the application of chemotherapy significantly reduced IgM levels *(Tab. 5, Ref. 28)*. Text in PDF *www.elis.sk*

KEY WORDS: COVID-19 pandemic, COVID-19 vaccine, cancer patients, radiotherapy, chemotherapy, SARS-CoV-2 IgM and IgG, abscopal effect.

Introduction

In the fight against the COVID-19 pandemic that emerged in 2019, immunization with vaccines was considered a promising approach (1). Cancer patients with weak immune systems were one of the most at-risk groups in this process. While the case/death rate for COVID-19 is 2.3 % in the general population, this rate more than doubles (5.6 %) in patients with cancer (2). It is known that the decrease in the absolute neutrophil count that may occur in cancer patients makes the patient especially vulnerable to bacterial infections. Lymphocyte depletion increases the risk of viral infection in this case (3). Cancer patients need to be protected more carefully against COVID-19 infection, as the surgery they undergo, chemotherapy (CT) and radiotherapy (RT) processes they receive make the patients cytopenic.

In the fight against COVID-19, vaccines are one of the most important and effective factors for ending the pandemic (4). The developed vaccines are used with emergency approval (5, 6). One of these vaccines, the Sinovac (CoronaVacR) vaccine produced in China against the Wuhan strain, became the first vaccine to be used almost all over the world (7, 8). Then, Pfizer/Biontech (BNT162b2) vaccines produced in Germany were made available. Sinovac is obtained by producing SARS-CoV-2 in cell culture and then by chemically inactivating the virus (9). Biontech, on the other hand, is an mRNA vaccine encoding the spike protein of SARS-CoV-2, which represents a completely new vaccine approach. The spike protein synthesized in the cell by reading the mRNA codes goes out of the cell and creates the desired immunity by stimulating both humoral (antibody) and cellular (T cell) immunity (10).

In this study, in which we sought answers to the questions relating to the immunological interaction of the tumor biology and vaccine, as well as to the immunosuppressive state caused by the treatment regardless of whether the vaccination per se or the vaccine type create protective antibodies or not, we investigated the

[1]Department of Radiation Oncology, Recep Tayyip Erdogan University Faculty of Medicine, Rize, Turkey, [2]Clinical Microbiology Department, Department, Faculty of Medicine Istanbul Medipol University, Istanbul, Turkey, and [3]Clinical Microbiology Department, Faculty of Medicine, Recep Tayyip Erdogan University, Rize, Turkey

Address for correspondence: Gonca Hanedan USLU, MD, Assoc Prof, Recep Tayyip Erdogan University Faculty of Medicine, Rize, Turkey. Phone: +090 5334291502**,** Fax: +904642123015

Acknowledgements: This work was supported by the Recep Tayyip Erdogan University, Coordination Unit for Projects of Scientific Research, Grant number Project ID/Code:1291/TSA-2021-1291.

IgM, IgG antibody levels formed by these vaccines administered to cancer patients and the parameters affecting it. We believe that it will contribute to establishing the operational guidance needed for the COVID-19 vaccine as well as to addressing the decisions regarding the use of vaccines against COVID-19, especially in oncology patients.

Materials and methods

After obtaining COVID-19 research approval from the Ministry of Health (2021-08-16T20_12_39), archive scanning permission from the Health Directorate (E-64247179-799/10.09.2021) and local ethics committee approval (E-40465587-050.01.04-247/17.11.2021), the project was carried out with the support financed by the Board of Scientific Research Projects Coordination (dated 18.11.2021, Project ID: 1291, Project Code: TSA-2021-1291).

Overall, 81 patients with oncological diagnoses, who were treated or followed up in our clinic and who received at least one dose of vaccine were included. Vaccination calendars and dates were searched retrospectively from the E-pulse system of the Ministry of Healthcare, which was recorded in a central system. WBC, neutrophil and lymphocyte values were noted from the blood tests of the patients during the vaccination period. The treatments received by patients, and various parameters such as age, gender, disease stage, type of vaccine administered and number of vaccines were recorded to investigate whether they had an effect on antibody formation.

Blood samples (2 ml) were taken for antibody measurement from the patients who came to the outpatient clinic examination. After the samples had coagulated at room temperature, they were centrifuged at 1,500 g, serum samples were separated, and SARS Cov-2 antibody test was applied on the same day. Tests were run on the Architect i1000sr with two-level quality control. Then, IgG and IgM measurements were performed separately using the chemiluminescent microparticle immunoassay (CMIA) method and the SARS-CoV-2 IgM and IgG II Quant (Abbott, Germany) quantitation kits. In accordance with the recommendations of the manufacturer, 0.99 AU /ml for Ig M and over 49 AU /ml for Ig G were evaluated as positive. These antibodies formed against the spike receptor binding site (RBD) of SARS were quantitatively measured to detect the antibody response of patients vaccinated against COVID-19.

Statistical analysis

Data were analyzed with IBM SPSS V23. Conformity to normal distribution was evaluated by Shapiro-Wilk and Kolmogorov-Smirnov tests. The Mann-Whitney U test was used to compare the data that were not normally distributed according to the paired groups. Spearman's rho correlation coefficient was used to examine the relationship between data with non-normal distribution. Binary logistic regression analysis was used to examine the risk factors affecting IgG and IgM values. Analysis results were presented as median (minimum – maximum) for quantitative data. Significance level was set as $p < 0.050$.

Results

Of the 81 patients included in the study, 23 (28.4 %) were female and 58 (71.6 %) were male. The mean age was 63 (29–max 86). Tumor localizations were as follows: lung (40.7 %), breast (21.0 %), prostate (16 %), and other rarer types (rectum, gynecological localization, bladder, etc.). The vast majority of patients (88.9 %) received RT, while 60.5 % received concomitant CRT.

There were 28 patients (34.6 %) who received two doses of vaccine and 48 patients (59.3 %) who received 3 doses of vaccine. The number of patients who had a single dose of vaccine was 5 (6.2 %). Four of these patients were vaccinated with Biontech

Tab. 1. Gender, stage of disease, and vaccination information of the patients.

Parameters		Number of patients	%
Gender	Female	23	28.4
	Male	58	71.6
Number of vaccines	dose 1	5	6.2
	doses 2	28	34.6
	doses 3	48	59.3
Vaccine type	Single Biontech dose	4	4.9
	Single Sinovac dose	1	1.2
	Only Biontech	11	13.6
	Only Sinovac	39	48.1
	Sinovac and Biontech	26	32.1
Disease stage	Early (stages 1–2)	19	23.5
	Late (stages 3–4)	62	76.5

Tab. 2. Risk factors affecting IgG negativity.

	Univariate		Multivariate	
	OR (%95 CI)	p	OR (%95 CI)	p
Gender	1.929 (0.383–9.699)	0.425	3.403 (0.445–26.047)	0.238
Age	0.969 (0.916–1.025)	0.266	0.974 (0.892–1.063)	0.554
Stage	0.79 (0.187–3.333)	0.748	0.692 (0.123–3.906)	0.677
Duration of period after 1st vaccine up to antibody measurement[1]	0.995 (0.985–1.004)	0.272	0.984 (0.965–1.004)	0.110
Biontech	0 (0–.)	0.997		
Sinovac	1.288 (0.642–2.585)	0.477	2.488 (0.911–6.795)	0.075
WBC during 1st vaccination period	0.982 (0.749–1.287)	0.893	0.948 (0.681–1.319)	0.752
NLR	0.777 (0.502–1.204)	0.259	0.799 (0.505–1.263)	0.336
Duration of last vaccine period up to antibody measurement[1]	0.889 (0.766–1.033)	0.126		
CT	1.886 (0.461–7.722)	0.378	2.219 (0.356–13.811)	0.393
RT	291315059.032 (0–.)	0.999		

Ab: Antibody, [1]: Days, WBC: White blood cell, NLR: Neutrophil Lymphocyte Ratio, CT: chemotherapy RT: Radiotherapy

Tab. 3. Risk factors affecting IgM antibody negativity.

Parameters	Univariate		Multivariate	
	OR (%95 CI)	p	OR (%95 CI)	p
Gender	1.508 (0.483–4.71)	0.480	1.843 (0.466–7.294)	0.384
Age	0.987 (0.939–1.037)	0.604	0.972 (0.897–1.053)	0.486
Stage	1.005 (0.285–3.547)	0.994	1.154 (0.275–4.841)	0.845
Duration of 1st vaccination period up to antibody measurement[1]	1.001 (0.992–1.009)	0.866	0.995 (0.976–1.015)	0.620
Biontech	0.644 (0.309–1.34)	0.239	1.257 (0.209–7.582)	0.803
Sinovac	1.331 (0.801–2.211)	0.269	1.932 (0.346–10.778)	0.453
WBC during 1st vaccination period	**1.333 (1.01–1.76)**	**0.042***	**1.344 (0.973–1.858)**	**0.073**
NLR	0.998 (0.87–1.144)	0.973	0.95 (0.812–1.111)	0.519
Duration of last vaccination period up to antibody measurement[1]	1.002 (0.978–1.025)	0.892		
CT	2.727 (0.912–8.152)	0.073	1.432 (0.372–5.521)	0.602
RT	3.631 (0.856–15.408)	0.080	2.483 (0.427–14.439)	0.311

Ab: Antibody, [1]: Day, WBC: White blood cell, NLR: Neutrophil/Lymphocyte Ratio, CT: Chemotherapy, RT: Radiotherapy. *p = 0.042, p < 0.050

Tab. 4. IgG and IgM antibody levels and quantitative parameters.

Parameters	IgG level		IgM level	
	r	p	r	p
Age	0.038	0.733	–0.045	0.689
Duration of 1st vaccination period up to antibody measurement[1]	0.105	0.350	–0.069	0.543
Biontech	0.525	**< 0.001***	0.172	0.124
Sinovac	–0.210	0.060	–0.147	0.189
WBC after 1st vaccination	–0.155	0.168	–0.251	**0.024****
NLR	0.146	0.193	0.104	0.356
Duration of last vaccination period up to antibody measurement[1]	0.014	0.927	0.051	0.732

r: Spearman's rho correlation coefficient. Ab: Antibody, [1]: Day, WBC: White blood cell, NLR: Neutrophil/Lymphocyte Ratio, *r = 0.525; p < 0.001, **r = –0.251; p = 0.02

Tab. 5. Factors affecting IgG and IgM levels.

Factors / Parameters		IgG level AU/ml Mean (min- max)	IgM level AU/ml Mean (min- max)
Gender	Female	1756.00 (2.00–40000)	0.26 (0.02–4.19)
	Male	795.05 (2.10–40000)	0.115 (0.03–15.8)
	Test statistics	U = 482.00	U = 595.00
		p = 0.053	p = 0.450
Stage	1-2	370.50 (16–40000)	0.10 (0.02–2.93)
	3-4	1552.05 (2–40000)	0.21 (0.03–15.8)
	Test statistics	U = 410.50	U = 545.00
		p = 0.047*	p = 0.624
CT	None	1044.75 (16–40000)	0.35 (0.03–15.8)
	Applied	1278.50 (2–40000)	0.11 (0.02–6.75)
	Test statistics	U = 756.50	U = 575.50
		p = 0.790	p = 0.044**
RT	None	2278.00 (353.20–40000)	0.33 (0.07–15.8)
	Applied	1044.75 (2.00–40000)	0.12 (0.02–6.75)
	Test statistics	U = 211.00	U = 206.00
		P = 0.089	p = 0.076

U: Mann–Whitney U test statistic, Mean (min–max), CT: Chemotherapy, RT: Radiotherapy, * p = 0.047, * ** p = 0.044

and one with Sinovac vaccine. There were 11 patients (13.6 %) vaccinated only with Biontech vaccines and 39 patients (48.1 %) only with Sinovac. Twenty-six (32.1 %) of the patients were vaccinated with vaccines of both producers. Gender, cancer stage and vaccination information of the patients are shown in Table 1.

Antibody tests were performed 62 days (7–123 days) on average after the last vaccination date of the patients. In a patient who received a single dose of Sinovac, the IgG value (23 AU/ml) measured 26 days later was negative. IgG values of 4 patients who received a single dose of Biontech, were 13884 AU/ml, 353AU/ml, 1383AU/ml and 11680AU/ml on days 20, 33, 48 and 71, respectively.

The mean WBC levels were 6.01 (10^3/uL) (1.36–14.68) after one dose of vaccine, 5.73 (10^3/uL) (2.39–18.48) after the second vaccine, and 5.54 (10^3/uL) (2.39–18.48) after the third vaccine. The respective neutrophil/lymphocyte ratios were 3.12 (0.60–32.82), 2.72 (1.00–10.09) and 2.96 (0.51–9.71. Respective lymphocyte levels were 1.20 (10^3/uL) (0.28–3.76), 1.20 (10^3/uL) (0.35–4.45) and 1.21 (10^3/uL) (0.34–3.55).

Factors potentially affecting IgG levels, namely age, gender, disease stage, time elapsed between vaccination and antibody measurement, type of vaccine, and CT and RT statuses were evaluated. There was no significant risk factor affecting IgG antibody negativity (p > 0.050). Variables were obtained as independent risk factors (Tab. 2).

WBC value after the first vaccination was found to be statistically significant as a risk factor affecting IgM antibody negativity (p = 0.042). When the WBC values in the period after the first vaccination increased by one unit, the risk of IgM negativity increased 1.333 times. Other variables were not obtained as risk factors (p > 0.050) (Tab. 3).

A significant, positive correlation was found between the number of Biontech vaccine doses and IgG antibody level (r = 0.525; p < 0.001). IgG level was higher in patients who received the Biontech vaccine. This increase was not dependent on any of evaluated factors. A statistically significant negative correlation was found between IgM antibody level and WBC value after the first vaccination (r = –0.251; p = 0.024). There was no statistically significant relationship between IgG and M levels and other variables (p > 0.050) (Tab. 4).

Mean IgG levels differ statistically according to the disease stage (p = 0.047). The mean level of IgG in stages 1 and 2 was 370.5, while that in stages 3 and 4 was 1552.05. Antibody formation in advanced stages (stages 3 and 4) was higher than in early-stage patients.

The mean IgM levels of the patients who underwent CT were found to be statistically low (p = 0.044). While it was 0.11 AU/ml in patients who underwent CT, it was 0.355 AU/ml in pa-

tients who did not. There was no difference in the mean levels of IgG and IgM relative to gender and RT status ($p > 0.050$) (Tab. 5).

Discussion

After the COVID-19 pandemic that emerged from the city of Wuhan, China, the Chinese Center for Disease Control and Prevention reported that 5.6 % of the case fatality rate among COVID-19 patients were people with cancer (11). In a study, it was shown that cancer patients have a high mortality rate with the risk of transmission and infection due to immunosuppression (12). It has been observed that cancer patients have a higher risk of COVID-19 infection compared to non-cancer patients (13).

SARS-CoV-2 exhibits a spread that is unusual for a respiratory virus due to its ability to bind to angiotensin-converting enzyme 2 (ACE2), a receptor expressed on almost all organ cells (14). Therefore, unlike most respiratory viruses, SARS-CoV-2 has a wider biodistribution and can cause significant damage outside the respiratory tract. Therefore, since most of the pathology after viremia is outside the airway, a vaccine that elicits IgG antibodies may protect patients against viremia. IgG antibody contributes to both viral neutralization and opsonization. It is effective in antibody and complement-dependent cell cytotoxicity (15).

The protection from viral infections is mainly provided by virus-neutralizing antibodies. Vaccine studies were accelerated by using structural and enzymatic proteins of SARS-CoV-2, genetically modified dendritic cells, infusion of antigen-specific T cells and mRNA encapsulated lipid nanoparticles encoding spike proteins, as well as plasmids encoding spike proteins and recombinant adenovirus. Some studies have been done using inactivated SARS CoV-2. The receptor-binding domain (RBD) in the S protein of the virus binds the cellular receptor, ACE2. Most antibodies that can neutralize coronaviruses are directed against the RBD and block the viral binding to ACE2 (16). Producing vaccine-induced antibodies against RBD has been the method used by the majority of COVID-19 vaccine studies (17).

Active immunity against various viral diseases is achieved by activating adaptive immunity. This is related to the body's exposure to the antigen and its duration. The adaptive response takes days/weeks to develop, but it lasts for a long time, in some cases for life. In this way, immunization, including vaccines, stimulates the individual's immune system to produce antibodies and lymphocytes. The immune system stimulated in this way triggers both humoral and cell-mediated immunity. These cells include T cells (cytotoxic T cells, helper T cells, memory T cells and suppressor T cells), B cells (memory B cells and plasma cells), and antigen-presenting cells (B cells, dendritic cells and macrophages). It involves the production of antibodies induced by the antigen/pathogen and causes the formation of long-term memory cells. Initial exposure elicits a primary response, and subsequent exposure to the same pathogen produces a much faster and stronger secondary response. As a result, acquired immunity occurs in response to exposure to an infection, and artificial immunity occurs through vaccination (18, 19). In immunosuppressive conditions that occur for various reasons, the effectiveness of acquired immunity is compromised.

Studies investigating the safety and efficacy of vaccines in immunocompromised cancer patients are limited. This has led to incomplete guidelines and data regarding the vaccination of cancer patients (20). Cancer patients can be divided into two groups, namely as severely or mildly immunosuppressed. Those who actively receive RT and/or CT are defined as 'patients with severe immunosuppression, while those who receive maintenance chemotherapy are classified as 'patients with mild immunosuppression' (21). It also means that developing an effective vaccine against pathogens like SARS CoV-2 in cancer patients in both categories can be difficult. The presence of active cancer and the cytotoxic treatments taken suppress the immune system.

In our study, the mean post-vaccine IgM levels of the patients who underwent CT were found to be statistically low ($p = 0.044$). Gender and RT status did not cause significant differences in mean IgG and IgM levels. This was thought to be associated with systemic CT being more immunosuppressive than RT, involving lower WBC values. In addition, in our study, WBC value after the first vaccination was found to be a risk factor affecting IgM antibody negativity ($p = 0.042$). When the WBC values in the period after the first vaccination increased by one unit, the risk of IgM negativity increased 1.333 times. This situation may be related to the improvement in the acute infection situation with the increase in WBC and conversion of active immunity to IgG-generating protective immunity.

In our study, it was shown that the disease stage significantly affected IgG levels ($p = 0.047$). The mean level of IgG in stages 1 and 2 was 370.5, while that in stages 3 and 4 was 1552.05. IgG antibody formation was higher in advanced cancer patients than in early-stage patients. This may be due to the complex structure of the immune system. Decades of research have also shown that chemotherapy can play different roles in anti-tumor immunity (22). Cancer immunology is characterized by antitumor T cells with reduced function and immunosuppressive tumor microenvironment (23). However, frequent administration of chemotherapeutic agents in non-toxic doses and without long rest periods has been defined as metronomic CT. Although this situation is designed to overcome drug resistance, it is reported to provide anti-tumor effective immunity (24). It is known that RT and CT immunotherapies increase their effectiveness and cause abscopal effect (25). Similar to chemotherapy, RT also induces immune cell death with direct cytotoxic effects (26). The cell death mechanisms of ionizing radiation are classically summarized as the 5Rs of radiobiology: repair of radiation damage, increased cell proliferation after radiation, redistribution of cell cycle, reoxygenation, and radiosensitivity. The most representative mechanism, by which RT kills tumor cells, is irreparable damage to double-stranded DNA. In addition, RT can initiate anti-tumor responses away from the irradiated area, known as the abscopal effect (27). Abscopal effect may contribute to the activation of the immune system. RT, CT, or both can increase the antibody response by stimulating the immune system as a result of the damage they cause.

Some studies have been conducted to develop guidelines for the COVID-19 vaccine administration in cancer patients (28). Accordingly, vaccinations are recommended to be done 1-2 weeks before or after RT and/or CT applications. With the exception of whole-body radiation, vaccination may need to be delayed as immune restructuring takes time. In addition, based on data from a study on optimal timing of influenza vaccination, it has been recommended that the COVID-19 vaccine be administered between 3-week chemotherapy cycles. As a result, it has been shown that the antibody response to the vaccine is similar in patients vaccinated simultaneously with chemotherapy and in patients vaccinated during the cytopenic period of the chemotherapy cycle (28).

In accordance with the regulations prepared by the Ministry of Healthcare in our country, oncology patients were sequentially vaccinated. In the meantime, as stated above, vaccination was carried out as soon as the vaccine was available during the RT/CT application or between the 3-week periods. While the first administrations of vaccines had been carried out with the Sinovac vaccine, later, when Biontech vaccine became available, the vaccines were administered by the patient's preference. A significant, positive correlation was found between the number of Biontech vaccine doses and IgG antibody level ($r = 0.525$; $p < 0.001$). IgG level was higher in patients who received the Biontech vaccine. This increase was not dependent on any of factors. A statistically significant, negative correlation was found between IgM antibody level and WBC counts after first vaccination ($r = –0.251$; $p = 0.024$). There was no statistical correlation between IgG and M levels and other variables ($p > 0.050$). With these data, we determined that the Biontech vaccine had a stronger effect on antibodies production in oncology patients.

Conclusions

IgG levels were significantly higher in oncology patients who received the Biontech vaccine than in those who received Sinovac. While chemotherapy was the factor that decreased the mean IgM level, advanced disease (stages 3 and 4) increased the mean IgG level. No significant correlation was found between the parameters such as gender, age, vaccination date, antibody test date, and neutrophil/lymphocyte ratio. A statistically significant, negative correlation was found between IgM antibody level and WBC count after first vaccination. This study helps establish operational guidance in the use of vaccines against COVID-19 in oncology patients.

References

1. COVID W. Vaccine Tracker and Landscape. Geneva: World Health Organization October 19: 2020.

2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395 (10229): 1054–1062. DOI: 10.1016/S0140-6736 (20)30566-3.

3. Steele TA. Chemotherapy-induced immunosuppression and reconstitution of immune function. Leukemia Research 2002; 26 (4): 411–414. DOI: 10.1016/s0145-2126 (01)00138-2.

4. Velipasaoglu S. Vaccine Immunity and Factors Associated with Response to Vaccines. Osmangazi J Med 2020: 1–5. DOI: 10.20515/otd.676787.

5. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. New Engl J Med 2020; 383 (27): 2603–2615. DOI: 10.1056/NEJMoa2034577.

6. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. New Engl J Med 2020; 384 (5): 403–416. DOI: 10.1056/NEJMoa2035389.

7. Wu Z, Hu Y, Xu M, Chen Z, Yang W, Jiang Z et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infectious Dis 2021; 21 (6): 803–812. DOI: 10.1016/S1473-3099 (20)30987-7.

8. TR Ministry of Health. Covid-19 vaccine information platform. Access Date 14.07.2021. https://covid19asi.saglik.gov.tr/.

9. Kritharis A, Tamer IM, Yadav VG. Vaccine production and supply need a paradigm change. Canad J Chem Engineer 2022; 10.1002/cjce.24399. DOI: 10.1002/cjce.24399.

10. Yu J, Tostanoski LH, Peter L, Mercado NB, McMahan K, Mahrokhian SH et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science 2020; 369 (6505): 806–811. DOI: 10.1126/science.abc6284.

11. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323 (13): 1239–1242. DOI: 10.1001/jama.2020.2648.

12. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol2020; 31 (7): 894–901. DOI: 10.1016/j.annonc.2020.03.296.

13. Liang W, Guan W, Chen R, Wang W, Li J, Xu K et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21 (3): 335–337. DOI: 10.1016/S1470-2045 (20)30096-6.

14. Zhang Y, Geng X, Tan Y, Li Q, Xu C, Xu J et al. New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. Biomed Pharmacother 2020; 127: 110195. DOI: 10.1016/j.biopha.2020.110195.

15. Janeway Jr CA, Travers P, Walport M, Shlomchik MJ. The distribution and functions of immunoglobulin isotypes. Immunobiology: The Immune System in Health and Disease 5th edition: Garland Science; 2001.

16. Barnes CO, West Jr AP, Huey-Tubman KE, Hoffmann MA, Sharaf NG, Hoffman PR et al. Structures of human antibodies bound to SARS-CoV-2 spike reveal common epitopes and recurrent features of antibodies. Cell 2020; 182 (4): 828–842. e16. DOI: 10.1016/j.cell.2020.06.025.

17. Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe 2020; 27 (3): 325–328. DOI: 10.1016/j.chom.2020.02.001.

18. Baxter D. Active and passive immunization for cancer. Human Vaccines Immunother 2014; 10 (7): 2123–2129. DOI: 10.4161/hv.29604.

19. Baxter D. Active and passive immunity, vaccine types, excipients and licensing. Occup Med 2007; 57 (8): 552–556. DOI: 10.1093/occmed/kqm110.

20. Plotkin SA, Orenstein W, Offit PA. Vaccines E-book: Elsevier Health Sciences; 2012.

21. Pickering L, Baker C, Kimberlin D, Long S, Pediatrics AAo. Red Book: 2012. Report of the Committee on Infection Diseases 29th ed, Elk Grove Village, IL: American Academy of Pediatrics 2012.

22. Bracci L, Schiavoni G, Sistigu A, Belardelli F. Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. Cell Death Differentiation 2014; 21 (1): 15–25. DOI: 10.1038/cdd.2013.67

23. Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science 2015; 348 (6230): 74–80. DOI: 10.1126/science.aaa6204.

24. Chen YL, Chang MC, Cheng WF. Metronomic chemotherapy and immunotherapy in cancer treatment. Cancer Lett 2017; 400: 282–292. DOI: 10.1016/j.canlet.2017.01.040.

25. Rakici SY. Chemotherapy and Radiotherapy in Cancer Treatment. Rize Med J 2021; 1 (1): 216–227.

26. El-Saghire H, Michaux A, Thierens H, Baatout S. Low doses of ionizing radiation induce immune-stimulatory responses in isolated human primary monocytes. Internat J Mol Med 2013; 32 (6): 1407–1414. DOI: 10.3892/ijmm.2013.1514.

27. Yu WD, Sun G, Li J, Xu J, Wang X. Mechanisms and therapeutic potentials of cancer immunotherapy in combination with radiotherapy and/or chemotherapy. Cancer Lett 2019; 452: 66–70.

28. Desai A, Gainor JF, Hegde A, Schram AM, Curigliano G, Pal S et al. COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials. Nature Rev Clin Oncol 2021; 18 (5): 313–319.

Received September 25, 2022.
Accepted October 11, 2022.