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SARS-CoV-2 neutralizing antibodies after first vaccination dose in breast cancer patients receiving CDK4/6 inhibitors

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ABSTRACT

Undoubtedly, the development of COVID-19 vaccines displays a critical step towards ending this devastating pandemic, considering their protective benefits in the general population. Yet, data regarding their efficacy and safety in cancer patients are limited. Herein we provide the initial analysis of immune responses after the first dose of vaccination in 21 breast cancer patients receiving cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors. The levels of neutralizing antibodies post vaccination were similar to the matched healthy controls, whereas no safety issues have been raised. Further exploration is needed to reduce the uncertainty of SARS-CoV-2 immunity among cancer patients under treatment.

1. Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, has a severe impact in every country of the world [1]. Vaccination process represents an effective mitigation measure [2]. Cancer patients face a higher risk of both severe infection and death [3] and have been prioritised to receive COVID-19 vaccination in several countries, including Greece. However, their exclusion from the confirmatory clinical trials [4] creates a gap in clinical data regarding the vaccines' efficacy and safety in this group of immunocompromised patients. In this context, we undertook a prospective study (NCT047443388) in order to investigate the immune response to COVID-19 vaccination in patients with hematological malignancies, solid tumours and healthy volunteers [5]. Herein, we present the analysis of SARS-CoV-2 neutralizing antibodies (NAbs) kinetics in breast cancer patients, receiving cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors.

2. Materials & methods

Inclusion criteria for the patient cohort included: (i) patients with histologically confirmed breast cancer under treatment with CDK4/6 inhibitors; (ii) age above 18 years; (iii) eligibility for vaccination. Both patients and healthy controls, known to be previously infected with COVID-19 virus, were excluded from the analysis.

Using an FDA approved assay (ELISA, cPass™ SARS-CoV-2 NAb Detection Kit; GenScript, Piscataway, NJ, USA) to measure SARS-CoV-2 NAbs, we analyzed serial blood samples, collected on day 1 (D1), prior to vaccination, and on day 22 (D22) post vaccination. The same ELISA plate was used for serum samples of the same patient or control subjects. The study was approved by the relevant Ethical Committees and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. Written informed consent was provided by each subject prior to enrollment. Baseline demographics, comorbidities, and the SARS-CoV-2 NAb levels have

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been compared between the study group and the control subjects; Chi-square test and Wilcoxon signed-rank test were applied for categorical variables or unpaired *t*-test and for continuous variables, respectively. To adjust for potential confounding variables, we used case-control matching to match the two groups for age and type of vaccine with the calipmatch command in Stata. All data extraction and analyses were conducted using Stata 16.0 (Stata Corp 2019, Stata Statistical Software: Release 16. College Station, TX: Stata Corp LLC). Two-sided p value < 0.05 was used for statistical significance.

3. Results

For this analysis of immunogenicity and safety, 21 female breast cancer patients with median age of 63 years (IQR: 46–76 years) and 160 controls (median age: 68 years; IQR: 58–82 years; $p = 0.101$ for age compared with patients), vaccinated during the same period, were enrolled. 20/21 (95.2%) patients and 135/160 (84.4%) controls were vaccinated with a mRNA vaccine (BNT162b2 and mRNA-1273), while one patient and 25 controls received the AZD1222 vaccine ($p = 0.18$). There was no significant difference in body mass index (BMI) between the two groups (mean BMI: 26.47 kg/m^2 in the study group and 26.48 kg/m^2 in the control group; $p = 0.99$). With regards to CDK4/6 inhibitor, 11 (52.4%) patients were treated with ribociclib, 7 (33.3%) with palbociclib, and the remaining 3 (14.3%) with abemaciclib. Comorbidities in the study group included diabetes mellitus in 9.52%, cardiovascular disease in 38.1%, and pulmonary disease in 4.76%. Summary of the main characteristics of the 21 patients included are demonstrated in Table 1.

On D1, no difference regarding the NAb titers between the two groups was observed ($p = 0.42$); 1 (4.76%) patient and 11 (6.9%) controls had a NAb titer of $\geq$30% (positivity cut-off). None had known history of COVID-19 infection.

On D22, after the first vaccine dose, NAb titers increased significantly in both breast cancer patients and controls (median NAb inhibition titer of 39.5% for patients and 42.83% for controls; $p = 0.45$). More specifically, 10/18 (55.6%) patients and 115/160 (71.9%) control subjects developed a NAb titer $\geq$30% on D22 ($p = 0.15$). In addition, the number of patients and controls who developed clinically relevant viral inhibition (NAb titers $\geq$50% [6] was 6/18 (33.3%) and 58/160 (36.2%) respectively. Of note, lymphopenia grade 1/2 and/or neutropenia grade 2/3 occurred in 5/21 (23.8%) patients prior to vaccination and were not associated with the D22 NAb titers (Fig. 1).

No safety issues linked targeted therapy administration was noted and the vaccines were well tolerated. In particular, 61.9% of patients reported no toxicities, while fever was the most common adverse effect of the vaccination, recorded in 19.1% of patients. No unexpected adverse events regarding the treatment with CDK4/6 inhibitors was noted during the post-vaccination follow-up period.

4. Discussion

Breast cancer represents a common malignancy of significant epidemiologic relevance among women. While, endocrine therapy (ET) has been historically the backbone of hormone receptor (HR)-positive disease, the recent advent of CDK4/6 inhibitors has transformed the therapeutic landscape of HR-positive and human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer [7]. Thus, these novel targeted therapies in combination with ET or fulvestrant are nowadays considered the standard of care for this subgroup of patients [8].

Yet, their administration during the pandemic remains an open debate, given the limited and inconsistent literature data regarding their safety. At first, a case-report of a middle-aged breast cancer patient with liver metastatic disease under CDK4/6 inhibition suggested that the short-term myelotoxic effect of palbociclib linked to delayed presentation of COVID-19 infection [9]. Later on, a

Table 1
Characteristics of the 21 breast cancer patients enrolled in the study.

#	Age	BMI	CDK4/6 inhibitor	CDK4/6 inhibitor dosage	Endocrine therapy	Months of treatment	Comorbidities	Lymphocytes (/μL)	Neutrophils (/μL)	Vaccine	Adverse events
1	82	20.2	Palbociclib	75 mg x1	Fulvestrant	26	Hypertension	1620	1500	BNT162b2	None
2	79	25.8	Palbociclib	125 mg x1	Letrozole	21	None	1100	1710	mRNA-1273	None
3	79	30.1	Palbociclib	75 mg x1	Letrozole	26	Hypertension, dyslipidemia	1500	990	BNT162b2	Pyrexia, arthralgia
4	64	36.1	Ribociclib	400 mg x1	Letrozole	30	Hypertension, dyslipidemia	1700	2000	AZD1222	Pyrexia
5	76	32.6	Ribociclib	600 mg x1	Letrozole	26	Diabetes mellitus, hypertension	700	2300	BNT162b2	None
6	39	24.8	Ribociclib	200 mg x1	Letrozole	13	None	1530	1350	BNT162b2	Pain at injection site
7	76	28.9	Palbociclib	125 mg x1	Fulvestrant	31	None	1700	1170	BNT162b2	None
8	45	23	Abemaciclib	150 mg x2	Tamoxifen	26	Hashimoto's thyroiditis	1600	2970	mRNA-1273	None
9	58	23.4	Ribociclib	600 mg x1	Letrozole	4	Hyperthyroidism	940	1640	BNT162b2	None
10	45	22.6	Abemaciclib	150 mg x2	Letrozole	24	Hypothyroidism	1550	2040	BNT162b2	None
11	67	30.2	Ribociclib	600 mg x1	Letrozole	2	Asthma	3200	2910	BNT162b2	Pyrexia
12	69	21.48	Palbociclib	100 mg x1	Fulvestrant	7	None	750	1950	mRNA-1273	Pyrexia
13	75	21.9	Ribociclib	400 mg x1	Letrozole	2	Hypertension, hypothyroidism, dyslipidemia, osteoporosis	1100	1770	BNT162b2	None
14	42	21.23	Ribociclib	600 mg x1	Letrozole	3	None	1240	780	BNT162b2	Headache
15	59	27.61	Ribociclib	600 mg x1	Fulvestrant	2	Diabetes mellitus, hypertension	1100	1170	BNT162b2	None
16	75	31.32	Ribociclib	600 mg x1	Letrozole	2	Systemic lupus erythematosus, hypertension, atrial fibrillation	2160	4180	BNT162b2	Fatigue, headache
17	76	26.86	Palbociclib	100 mg x1	Letrozole	15	None	850	940	BNT162b2	None
18	38	33.5	Ribociclib	400 mg x1	Letrozole	34	Hypothyroidism, Hodgkin lymphoma	1260	2560	BNT162b2	None
19	74	25	Palbociclib	125 mg x1	Fulvestrant	11	Myasthenia gravis, hypothyroidism, dyslipidemia	600	1410	BNT162b2	Fatigue
20	55	23.4	Ribociclib	600 mg x1	Fulvestrant	8	Hypothyroidism	2680	3250	BNT162b2	None
21	46	25.92	Abemaciclib	50 mg x2	Tamoxifen	25	None	1300	2810	BNT162b2	None

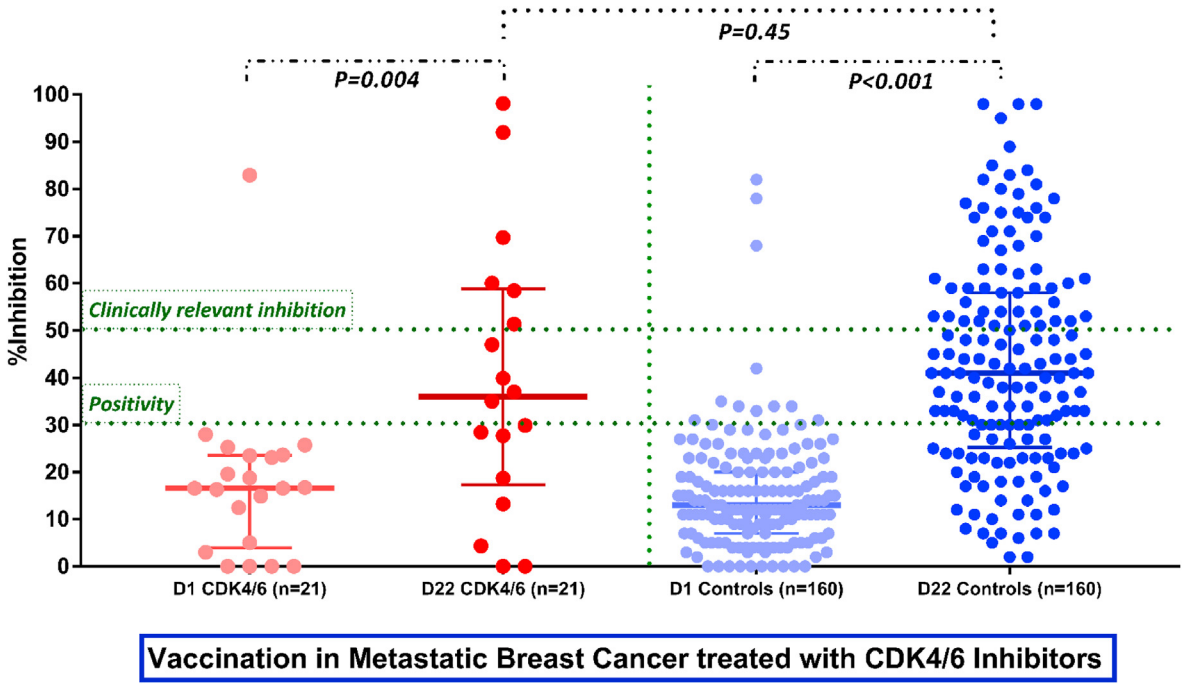

Fig. 1. Kinetics of the neutralizing antibodies in breast cancer patients receiving CDK4/6 inhibitors and matched controls, following the first dose of the BNT162b2, AZD1222, mRNA-1273 vaccines.

Spanish retrospective study conducted on 79 breast cancer patients demonstrated that either withdrawal or dose modification of CDK4/6 inhibitors might lead to a non-significant reduction in SARS-CoV-2 disease risk [10]. Recently, the experience of European cancer centers is indicative of a rather safe use of these targeted treatment modalities during the COVID-19 pandemic [11,12].

To the best of our knowledge, we provide the first insights into the immunogenicity and safety of COVID-19 vaccination in breast cancer patients receiving the first dose of BNT162b2, mRNA-1273, and AZD1222 vaccines, while on treatment with CDK4/6 inhibitors. Generally, all three vaccines were well tolerated in the study population and immune response up to day 22 was similar to the general population. It should be noted that almost one out of three breast cancer patients on CDK4/6 had developed clinical significantly immunity (NAb titers $\geq$50%) 3 weeks after vaccination. These results differ from the poor one-dose vaccine efficacy in cancer patients, reported by Monin et al. and Terpos et al. [13,14].

The more common side effects of CDK4/6 inhibitors palbociclib and ribociclib - due to their mechanism of action – are neutropenia and leukopenia [15]. However, this did not preclude immune response in these patients and no difference in the NAb titers among the three types of CDK4/6 inhibitors administered in our patients was noted. Noteworthy, there were neither specific timing issues nor treatment schedule changes; indeed, the included patients received the first dose of COVID-19 vaccine at any timepoint, during their treatment cycle, yet, every patient underwent a complete blood count the day prior to vaccination.

Despite the small size sample of our study, our data provide significant information regarding the optimal management of breast cancer patients treated with CDK4/6 inhibitors during vaccination for COVID-19. Ongoing recruitment and additional follow-up will allow further investigation of safety and efficacy of the vaccination as well as possible associations with factors related to the treatment or the disease.

5. Conclusions

Patients with breast cancer receiving CDK4/6 inhibitors develop SARS-CoV-2 NAbs in response to the first dose of COVID-19 vaccines, similarly to the general population.

Ethical approval

The study was approved by the respective Ethical Committees (Alexandra Hospital Ethics Committee, reference number: 900/24-12-2020) in accordance with the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. All patients and controls provided written informed consent prior enrollment in the study.

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Declaration of competing interest

The authors report no conflict of interest.

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