Humoral Immunity Response of COVID-19 Vaccine and Adverse Effect Among Solid Cancer Patient: A Prospective Cross-Sectional Study

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Abstract

Background and aim: Patients with cancer are at an increased risk for morbidity and mortality from coronavirus disease 2019 (COVID-19). Although cancer patients should have the priority for vaccination against SARS-CoV-2, data on vaccine immunogenicity and safety against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are scarce. The aim of this prospective study was to investigate the safety and efficacy of Pfizer-BioNTech's COVID-19 vaccine (BNT162b2) in solid cancer patients receiving active chemotherapy. Methods: We evaluated the safety and immunogenicity of BNT162b2 vaccine in 51 solid cancer patients undergoing active therapy in Azadi Hematology – Oncology center in Duhok city. The serum IgG antibody titer for S1 protein was measured by using VIDAS at pre-vaccination and 14-30 days after the second dose. The adverse events of vaccine were collected by a standardized questionnaire. Results: From 51 patients, most were metastatic (35, 68.63%), stage IV (28,54.90%). Females were more than males (36, 70.59%), (15, 29.41%) respectively. The most common types of cancer were breast (16, 31.37%), colon (8, 15.69%). Anti-S1 antibody level was significantly high. Fifty patients were seropositive (98.04%). Vaccine showed high safety profile; most of the adverse effects were mild to moderate. Most of the side effects recovered over 1-3 days. Injection site reactions were the most frequent local adverse effects after first and second doses, 17.6% and 52.9, respectively. On the other hand, most prevalent systemic adverse effects were fever (17.65%, 44.00%), headache (16.00%, 21.57%), and myalgia (35.29%, 5.88%) after first and second doses, respectively. Conclusion: the COVID-19 vaccine acceptance rate was high (89.36%). The seropositivity, following BNT162b2 vaccine, was extremely high (98.04) among cancer patient on active chemotherapy. The vaccine showed good tolerance and an excellent safety profile. Hence, it should be strongly recommended for such a risky vulnerable group to SARS-CoV-2. Breast cancer showed significantly higher seropositivity in comparison to colon cancer, which may be attributed to chemotherapy regimen, degree of immunosuppression, and gender factors.

Keywords: Solid cancer, COVID-19, vaccine, BNT162b2, immunogenicity, safety.

INTRODUCTION

Patients with cancer are at an increased risk for morbidity and mortality from SARS-CoV-2 (Dai et al., 2020, Kuderer et al., 2020), and active chemotherapy treatment may further abound these risks (Lee et al., 2020). During the beginning of the pandemic, a little was known about the risk of transmission and severity of SARS-CoV-2 among cancer patients, thus cancer management guidelines were revised, which, in turn, negatively impacted early cancer detection and resulted in a delayed treatment (Schrag et al., 2020). Patients with cancer have a higher risk of acquiring SARS-CoV-2 infection because of their immunocompromised status (Yu et al., 2020a). In a study of 1,524 cancer patients in a tertiary hospital in China, the prevalence of COVID-19 was twice higher in non-cancer patients (Yu et al., 2020b). Moreover, a cohort study of 928 patients from COVID-19 Cancer Consortium showed a 13% thirty day-all- cause death due to COVID-19, which was 10-13 times higher than in general population. In addition, the incidence of mortality was higher in active cancer patients on chemotherapy (Kuderer et al., 2020). Likewise, a meta-analysis of 52 studies included 18,650 cancer patients with COVID-19; the incidence of mortality was 25.6% (Saini et al., 2020). Therefore, it is important to build up immunity against the virus to prevent COVID-19 or attenuate its severity. The World Health Organization (WHO) licensed COVID-19 vaccines that have been proven effective against SARS-CoV-2 variants. In Duhok, Iraqi Kurdistan, three vaccines are approved for use, namely: Pfizer-BioNTech's COVID-19 vaccine (BNT162b2), Oxford-AstraZeneca ChAdOx1-S, and Sinopharm (BBIBP-CorV) (Abdulkader and Merza, 2022). BNT162b2 vaccine were administered in almost all solid tumor patients of Duhok. BNT162b2 vaccine showed 95% efficacy in preventing COVID-19 infection, including severe cases in phase 3 trial of the 18,860 vaccinated persons. However, patients with immunocompromised conditions including cancer, and those on

immunosuppressive therapy including chemotherapy have been among the exclusion criteria of the trial. Hence, it remains unclear how cancer patients on active chemotherapy will respond to BNT162b2 vaccine for induction of immunity; and vaccine safety was an additional concern (Vergnes, 2021, Corti and Curigliano, 2021). Although, the American Society for Clinical Oncology and the European Society for Medical Oncology is highly recommending vaccinating cancer patients treated with systemic cytotoxic therapy (Ligumsky et al., 2022), studies have demonstrated that SARS-CoV-2 antibodies was lower in solid cancer patients on active chemotherapy than in healthy volunteers after vaccination (Addeo et al., 2021, Barrière et al., 2021a, Massarweh et al., 2021). Hence, we aimed to perform this prospective study to investigate the safety and efficacy of BNT162b2 in solid cancer patients receiving active chemotherapy.

METHODOLOGY

Study Design

A prospective cross-sectional study was conducted at Azadi Hematology - Oncology center in Duhok city/Iraq Kurdistan from September 15, 2021 to June 1, 2022 to evaluate the immunogenicity and safety of BNT162b2 vaccine in solid cancer patients undergoing active intravenous chemotherapy.

Patient Population

All study populations were adults (≥ 18 years) with histologically confirmed solid cancer patients receiving active chemotherapy. Patients administered with BNT162b2 vaccine were included. Exclusion criteria were: known history of COVID-19 infection, positive SARS-CoV-2 IgG, patients on immunotherapy, hormonal therapy, targeted therapy, and radio therapy. COVID-19 vaccine was offered to all solid cancer patients visiting Azadi Hematology - Oncology center. The patients were vaccinated according to the Kurdistan national program in different vaccination centers at Duhok province. An informed consent was obtained from patients who participated in the study. The study was approved by local ethics committee on November, 2021. under reference number (10112021-11-15).

Time of Vaccination

The vaccine was administrated to patients 7-14 days before or after their therapy. All patients received 2 doses of the BNT162b2 vaccine as recommended by manufacturer at a 21-day interval. All patients underwent complete blood counts before vaccination and administration was deferred in those with low neutrophil until it returned to normal (Cavanna et al., 2021).

Serological Assessment

Serum samples have been analyzed immediately after collection. Serum IgG of SARS-CoV-2 was measured by an automated technique (Vidas SARS-CoV-2 IgG, biomérieux, France) with an enzyme linked fluorescent assay (ELFA). IgG against the receptor binding domain (RBD) of SARS-S-CoV-2 spike protein was detected by Vidas SARS-CoV-2. An index (≥ 1.00 = positive) was used to report quantitative findings (Renard et al., 2021). The first blood sample was tested for IgG antibody assessment up to two days before the first vaccination dose and the second blood sample was taken 14-30 days after the second vaccine dose (Cavanna et al., 2021, Karacin et al., 2021).

Endpoints

The primary endpoint was to evaluate the immunogenicity of BNT162b2 vaccine in solid cancer patients on active systemic anti-cancer therapy. The secondary endpoint was to assess side effects, safety, and factors affecting the vaccine immunogenicity in solid tumor patients including age, gender, type and stage of cancer, type of chemotherapy (Karacin et al., 2021).

Safety of Vaccine

Local and systemic adverse events of the vaccine were assessed by face-to-face or telephone consultation. Adverse effects were graded to four scales as follows (Monin et al., 2021): grade 1 (mild; does not affect daily activities), grade 2 (moderate; interferes with daily activities), grade 3 (severe; prohibits daily activities), and grade 4 (life-threatening: requires emergency department visit and/or hospital admission).

Statistical analyses

The general information of these cancer patients was presented in number and percent, or mean and standard deviation. The incidence of side effects of COVID-19 vaccines and prevalence of cancer types and stages were determined in number and percent. The comparisons of IgG levels between and after COVID-19 vaccination in cancer patients were examined in a paired t-test. The comparisons of IgG levels among cancer patients with different characteristics were examined in ANOVA one-way or by an independent t-test. The significant level of difference was determined by a p-value <0.05. The statistical calculations were performed in JMP pro14.3.0.

RESULTS

Patient characteristics

Three hundred seventy-two patients on active chemotherapy who visited Azadi Hematology – Oncology Center have been offered BNT162b2 vaccine as shown in (Fig 1). Out of those, 51 fulfilled full vaccination. The median patient age was 51.98 years (range: 19-70), 80.39% were above 40 years, and 70.59% were female. The most common type of cancers were breast, colon and ovarian cancer, 31.37%, 15.69%, 9.8% respectively. The majority of patients (82.35%) were without co-morbidity. Metastatic disease status and stage IV were presented in 68.63% and 54.9% of patients, respectively. Baseline characteristics of patients are presented in Table 1.

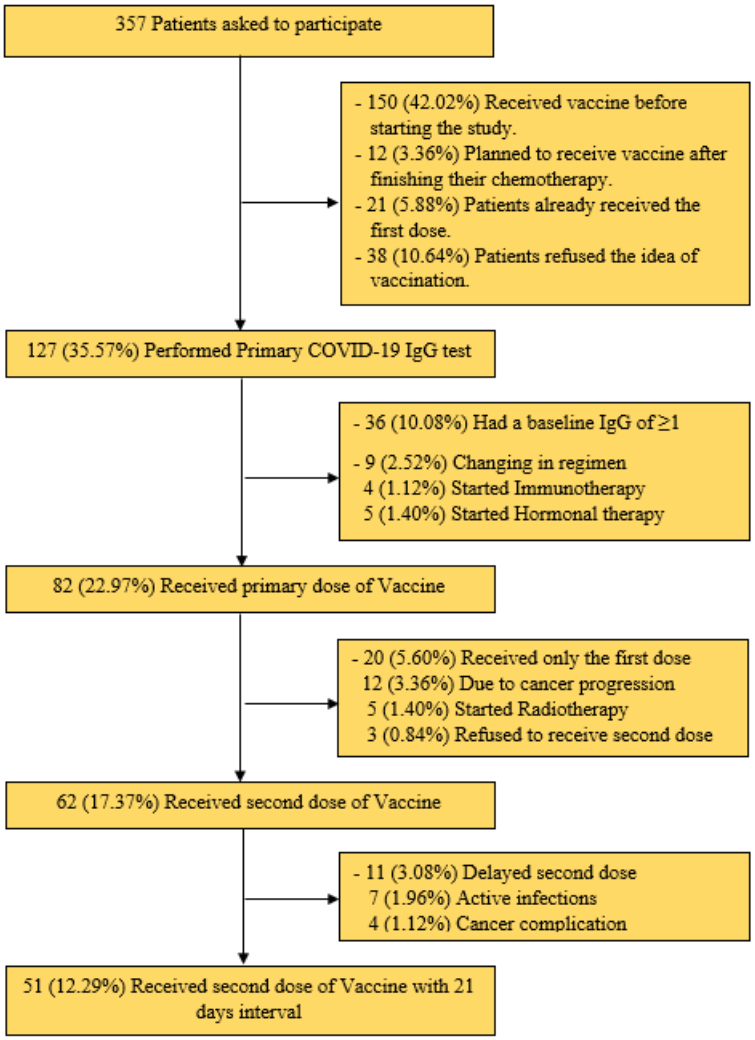

Figure 1 Flow chart of the patients included in the study

Table 1: Demographic and medical characteristics of cancer patients

Characteristics (n=51)	**Number**	**Percent**
Age (19-72 years) mean (SD)	51.98	11.64
Age groups		
19-30	1	1.96
31-40	9	17.65
41-50	14	27.45
51-60	13	25.49
61-70	14	27.45

Sex		
Male	15	29.41
Female	36	70.59
Co-morbidity		
No comorbidity	42	82.35
Diabetes, Hypertension	3	5.88
IHD, Hypertension	2	3.92
Hypothyroidism	1	1.96
Hypertension	2	3.92
Diabetes	1	1.96
Cancer stage		
II	8	15.69
III	15	29.41
IV	28	54.90
Disease Status		
Localized/Respectable	16	31.37
Advanced/Metastatic	35	68.63
Cancer type		
Bladder Cancer	1	1.96
Breast Cancer	16	31.37
Colon Cancer	8	15.69
Endometrium Cancer	2	3.92
Esophageal Cancer	2	3.92
Gall Bladder Cancer	1	1.96
Gastric Cancer	3	5.88
HCC	1	1.96
Head & Neck Cancer	1	1.96
Laryngeal Cancer	2	3.92
Liver Cancer	3	5.88
Ovarian Cancer	5	9.80
Pancreatic Cancer	2	3.92
Rectum Cancer	2	3.92
Small Cell Lung Carcinoma	1	1.96
Soft Tissue Sarcoma	1	1.96

Immunogenicity

Of the 51 patients, 50 (98.04%) showed seroconversion, while only one patient (1.96%) at stage four head and neck cancer who received cetuximab, cisplatin, and fluorouracil was seronegative after the second vaccination dose Table 2. All types of cancers showed seropositivity; however, in term of cancer types frequency, breast cancer showed significantly higher seropositivity (P=0081). Other various characteristics, including stage of the disease, age, sex, co-morbidities, and type of chemotherapy, showed no significant differences table 3.

Table 2: Comparisons of IgG levels between and after COVID-19 vaccination in cancer patients

	IgG level		**Mean difference (95% CI)**	**p-value**
	Before treatment	**After treatment**		
IgG	0.32 (0.32)	31.86 (16.75)	31.54 (26.84 to 36.24)	**<0.0001**
IgG outcome				
Positive	0 (0.0)	50 (98.04)	98.04%	NA
Negative	51 (100)	1 (1.96)		
A paired t-test was performed for statistical analysis.				

Table 3: ANOVA one-way and an independent t-test for Comparisons of IgG levels among cancer patients with different characteristics

Characteristics (n=51)	**Statistics**		**P-value (two-sided)**
	Mean	**Std Dev**	
Cancer stage			0.4619[a]
II	25.83	19.84	

III	30.92	15.25	
IV	34.10	16.76	
Disease Status			0.7521[b]
Localized/Respectable	30.75	15.32	
Advanced/Metastatic	32.37	17.56	
Sex			0.2379[b]
Male	36.19	17.40	
Female	30.06	16.38	
Age category			0.1784[a]
19-30	41.39	.	
31-40	44.41	8.58	
41-50	27.09	17.47	
51-60	32.04	15.32	
61-70	30.89	17.63	
Cancer type			0.0081[b]
Breast Cancer	26.88	16.92	
Colon Cancer	46.37	6.35	
Comorbidity			0.4271
No comorbidity	33.94	16.63	
Diabetes, Hypertension	20.99	10.90	
IHD, Hypertension	28.61	27.75	
Hypothyroidism	9.05	.	
Hypertension	19.03	16.57	
Diabetes	32.53	.	
[a] ANOVA one-way and [b] an independent t-test were performed for statistical analyses. *The sub-category has one patient only. It has not Sta. deviation.			

Side Effects

Injection site reactions (pain, erythema, and swelling) were the most frequent local adverse effects after first and second vaccine doses, 17.6% and 52.9, respectively. On the other hand, most prevalent systemic adverse effects were fever (17.65%, 44.00%) and headache (16.00%, 21.57%), after first and second doses, respectively. Myalgia was most common in the second dose (35.29%), compared to the first dose (5.88%) of vaccination. The frequency of side effects was more defined after the second dose (table 4). Frequently reported adverse effects were mild to moderate. Only two patients (3.90%) after the first dose and one patient (1.96%) following the second dose developed severe reactions (table 5). The adverse effects were recovered in 19 (37.26%) patients after the first dose and 21(41.18%) after the second dose over 1 – 3 days; only 5 (9.80%) patients required more than 7 days (table 6).

Table 4: Side effects of cancer patients after first and second doses of COVID-19 vaccine

Side effects (n=51)	**No side effect**		**With side effects**	
Side effects after the first dose	**Number**	**Percent**	**Number**	**Percent**
Fever	42	82.35	9	17.65
Injection site reaction (pain, redness, and swelling)	42	82.40	9	17.60
Headache	42	84.00	8	16.00
Myalgia and muscle pain	48	94.12	3	5.88
Chills	48	94.10	3	5.90
Diarrhea	50	98.00	1	2.00
Flu-Like Symptoms	50	98.00	1	2.00
Nausea and vomiting	48	94.10	3	5.90
Side effects after the second dose				
Fever	28	56.00	22	44.00
Injection site reaction (pain, redness, and swelling)	24	47.10	27	52.90
Headache	40	78.43	11	21.57
Myalgia and muscle pain	33	64.71	18	35.29
Chills	45	88.20	6	11.80
Diarrhea	49	96.10	2	3.90
Flu-Like Symptoms	50	98.00	1	2.00

Nausea and vomiting	49	96.10	2	3.90

Table 5: Severity of side effects after first and second dose of vaccine

Characteristics (n=51)	**Statistics**	
	Number	**Percent**
Severity of symptoms first dose		
No symptoms	26	50.90
mild	15	29.40
moderate	8	15.60
severe	2	3.90
Severity of Symptoms second dose		
No symptoms	15	29.40
Mild	25	49.00
moderate	10	19.60
severe	1	1.96

Table 6: ANOVA one-way for durations of symptoms after the first and second dose.

Duration (n=51)	**Frequency distribution**		**IgG**	
	Count	**Percent**	**Mean (SD)**	**p-value**
After first dose				0.7247
No symptom	27	52.94	33.74 (17.28)	
1-3 days	19	37.26	30.37 (17.61)	
≥4 days	5	9.80	28.51 (13.83)	
After second dose				0.6044
No symptom	16	31.37	28.25 (16.49)	
1-3 days	21	41.18	35.74 (15.19)	
4-7 days	9	17.65	31.93 (19.14)	
>7 days	5	9.80	29.16 (22.61)	

DISCUSSION

In this prospective study we evaluated the humoral immunity response and safety of the BNT162b2 vaccine in solid cancer patients receiving active chemotherapy. Although the evidence is not yet conclusive, SARS-CoV-2 humoral immunity response is considered as "correlate of protection" against infections with COVID-19 severe disease (Lumley et al., 2021). Recently published researches demonstrate the correlation between humoral immunity response and COVID-19 protection in healthy populations and cancer patients, suggesting the use of post vaccination antibody response to evaluate vaccine efficacy (Massarweh et al., 2021, Earle et al., 2021).

In this study, BNT-162b2 vaccine was very effective (98.04%), which was in parallel with other studies from Japan (98.4%) (Yamasaki et al., 2022), France (95.2%) (Barrière et al., 2021a), Greece (90.5%) (Linardou et al., 2021), and Switzerland (93%) (Addeo et al., 2021). On the contrary, a prospective study from Italy and a study from Israel reported seropositivity of 75.88% and 84.1%, respectively (Cavanna et al., 2021) (Shmueli et al., 2021). This low immunogenicity, in comparison to our study, is attributable to including patients on immunotherapy and biological therapy, which are known risk factors for reduced immunogenicity. Although few studies attributed low seropositivity to the male gender (Cavanna et al., 2021), we did not find such association.

In the current study, breast cancer showed significantly higher seropositivity in comparison to colon cancer (p=0.0081), which was consistent with findings from Linardou et. al. (Linardou et al., 2021). This may be attributed to chemotherapy regimen, degree of immunosuppression, and gender factors. Our data, along with the aforementioned studies, support the use of BNT162b2 vaccine in solid cancer patients on active treatment. The enrollment of miscellaneous solid cancer patients with different chemotherapy regimens, irrespective of disease stages and clinical characteristics, is a favorable marker for vaccinating solid cancer patients with BNT162b2 vaccine.

In this study, vaccine administration was well tolerated. The majority of patients showed mild to moderate adverse effects after the first and second doses, corresponding to 45% and 68.6%, respectively. This finding was in agreement to a prospective study from Italy including 257 solid tumors of whom 31.52% and 33.46% complained from mild to moderate adverse effects after first and second doses, respectively (Cavanna et al., 2021). Other observational studies for e.g. Monin et al. reported similar BNT162b2 vaccine tolerance profile (Monin et al., 2021). The favorable safety profile was documented during phases 1-3 testing of BNT-162b2 COVID-19 vaccine, with mild to moderate adverse effects being the most frequent (Polack et al., 2020, Walsh et al., 2020).

Similar study by our team on COVID-19 vaccine adverse effects on a community of Iraqi general participants revealed side effects in 84.8%, mostly of mild to moderate intensity (Almufty et al., 2021). Hence, our studies conclude that adverse effects of BNT162b2vaccine in cancer patients were less prominent than other non-cancer patients. In agreement, studies from Greece and the UK on cancer patients and healthy control showed more frequent side effects among the control groups (Linardou et al., 2021, Monin et al., 2021). The less frequent adverse effects among cancer patient is thought to be related to their immunocompromised status (Hause et al., 2022). In the present study, topical adverse effects, fever, myalgia, and headache were the most reported side effects. Correspondingly, several studies recorded a similar pattern (Linardou et al., 2021, Monin et al., 2021, Yamasaki et al., 2022). The duration of side effects in the majority of patients was 1-3 days. Only a few number patients complained from side effects occurring more than 7 days. This finding was concordant with a study from the UK that exhibited adverse effects in 1.6% of the patients 7 days post-vaccination (So et al., 2021). Therefore, BNT162b2 vaccine in cancer patients has an excellent safety profile and should be strongly recommended for such risky vulnerable groups to SARS-CoV-2.

It is worth mentioning that in our study, the vaccine acceptance rate was high (89.36%) with a vaccine refusal rate of 10.64%, which was in line to other studies that displayed refusal up to 10% (Di Noia et al., 2021, Barrière et al., 2021b, Mejri et al., 2022). A similar study from our region on general population revealed vaccine hesitancy in more than 50%, which was blamed on the adverse effects (Tahir et al., 2022). In comparison, the vaccine acceptance rate is higher among cancer patients, which could be due to the severe nature and poor prognosis of COVID-19 among such patients.

Despite the practicality and usefulness of this study, a few limitations are present. First, the sample size was small, which did not allow analyzing the immunogenicity precisely in patient subgroups including cancer types and treatment regimens. Second, although humoral immunity response is a strong measure for immunogenicity response, cellular immunity is also an important factor for protection against SARS-CoV-2 infection (Linardou et al., 2021), which has not been assessed in our study. Hence, further studies with larger sample sizes considering both humoral and cellular immunity are warranted to better understand the immunogenicity in cancer patients.

Conclusion

In keeping with recorded literatures, the COVID-19 vaccine acceptance rate was high (89.36%). The seropositivity following BNT162b2 vaccine was extremely high (98.04%) among cancer patient on active chemotherapy. The vaccine showed good tolerance and an excellent safety profile. Hence, it should be strongly recommended for such a risky vulnerable group to SARS-CoV-2. Breast cancer showed significantly higher seropositivity in comparison to colon cancer, which may be attributed to chemotherapy regimen, degree of immunosuppression, and gender factors.

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