

Value of Influenza Vaccines in Cancer Patients during the Coronavirus (COVID-19) Pandemic

Running title: Flu vaccine during the COVID-19 Pandemic

Abstract

Background & aims: According to the recommendation of the Centers for Disease Control and Prevention (CDC), getting *Influenza Vaccines* during the Coronavirus (COVID-19) pandemics is especially important for people with certain underlying medical conditions, like cancer. Due to the similarities between the symptoms of influenza and Covid-19, receiving the flu vaccine in suspicious cases can be helpful because it will make it easier to request a medical test and diagnosis. In this cross-sectional descriptive study, the value of influenza vaccination in the cancer population was investigated.

Subjects and Methods: All cancer patients who were referred to our clinic and had eligibility to receive the flu vaccine were included in our study for following up clinical signs every week for one month. All patients who were vaccinated from October 1 to 15, 2020, were investigated. The most side effects that were followed were fever, runny nose, bone pain, life-threatening, or persistent adverse effects.

Results: From a total of 289 patients [median age: 52 years (range 18-79), 112 (38.9 %) males and 176 (61.1%) female] with different types of cancers, only two patients had an adverse effect of vaccination (including bone pain, runny nose, and fatigue), and one had Covid-19 ten days after vaccination. The rest of the patients did not show any side effects due to flu vaccination after one month of follow-up.

Keywords: Influenza Vaccines; Cancer patient; COVID-19; Pandemics

Introduction

Getting a flu vaccine during the Coronavirus (COVID-19) pandemic is especially important for people with certain underlying medical conditions, like cancer. Cancer or its treatment can lower the resistance to infection and is more likely to catch the flu. The flu vaccination makes it less likely that cancer patients catch the flu. In cancer patients, active immunization has been shown to confer protective immunity against several infections at similar rates to healthy individuals, which has translated into decreased duration and severity of the infection and potentially improved morbidity and mortality (1). The Centers for Disease Control and Prevention (CDC) recommends annual flu vaccinations for high-risk populations, including health care workers, the elderly, and patients with immunodeficiency or chronic and malignant diseases. Influenza vaccines released this year (2019-2020) are quadrivalent, protecting against four different types of flu. For influenza A, the vaccine contains H3N2 and H1N1. For influenza B, it covers the Victoria lineage (a new type of influenza B) and the Yamagata lineage (2).

Before the coronavirus pandemic, less than 50% of patients receiving chemotherapy typically received influenza vaccination (3, 4). On the other hand, due to the similarities between the symptoms of influenza and Covid-19, receiving the flu vaccine in suspicious cases can be helpful because it will make it easier to request a medical test and diagnosis.

The prevalence of this pandemic raises the question of whether it is safe to receive the flu vaccine even during a coronavirus pandemic in high-risk individuals such as cancer patients. This study was performed to evaluate the value of influenza vaccination in the cancer population.

Subject and methods

Procedures adopted in this study have been approved by the local ethics committee and are according to the Declaration of Helsinki principles.

In this cross-sectional descriptive study, all cancer patients who were referred to our clinic and had eligibility to receive the flu vaccine (*Influvac TETRA 2020/2021 Surface antigen/inactivate, Abbott Biological B.V Netherlands*) were included in our study for following up clinical signs every week for one month. All patients who were vaccinated (one 0.5 ml dose) from October 1 to 15, 2020, were investigated. In terms of cancer type, patients were divided into two categories, hematologic cancer (including multiple myeloma, lymphoma, and Hodgkin's disease) and solid cancer (other than hematological) (Table 1).

However, most patients with most hematologic malignancy were not candidates for the vaccine due to the type of treatment they received, such as *rituximab*. The time for vaccination in those who had received chemotherapy every 3 weeks was the end of the third week and before the start of a new course of chemotherapy, although the new term was postponed for 4 days. The same is true for two-week treatments. Patients were evaluated for white blood cell (WBC) counts before receiving the vaccine, and only those with $>3000/\text{mm}^3$ WBC were vaccinated.

Side effects listed in the vaccine leaflet, such as headache, fatigue, sweating, myalgia, arthralgia, malaise, local reactions, and shivering (5), were common complications that could occur in cancer patients due to either disease or chemotherapy. For this reason, the most side effects that were followed were fever, bone pain, life-threatening, or persistent adverse effects.

Data were analyzed using SPSS 22 statistical software and reported as frequency (percentage) and mean (\pm standard deviation).

Results

A total of 289 patients [median age: 52 years (range 18-79), 112 (38.9 %) males and 176 (61.1%) female] were included. They were under chemotherapy for biliary tract (2.4%), bladder (1%), breast (37.2%), cervix (0.7%), Gastrointestinal (29.5%), lung (4.9%), melanoma (0.7%), ovarian (2.1%), pancreas (2.1%), salivary and parotid (0.7%), testis and prostate (1.4%), and hematological cancers (10.1%) (Table1). Out of 289 patients under study, one patient did not receive the vaccine due to egg allergy. Five patients under rituximab therapy did not experience any side effects after receiving the flu vaccine (Table 2). To explain that, these patients without coordination with the oncologist had received the flu vaccine from the regional health center. Patients with comorbidities other than cancer (including Liver transplant, Congestive heart failure, Rheumatoid arthritis, and Renal Failure) also reported no side effects within a month after receiving the flu vaccine.

Three patients with colon cancer and one patient with multiple myeloma had a history of Covid-19. These patients were well after receiving the flu vaccine. One of the patients with biliary tract cancer, due to the involvement of patient caregivers, became infected with coronavirus after receiving the flu vaccine, which returned to normal after a few days. One case of patients with colon cancer (grade IV) and a history of COVID-19, suffered from the vaccine's side effects such as bone pain, fatigue, and runny nose. Besides, a patient with metastatic breast cancer (grade IV) had significant side effects 4 days after receiving the vaccine, which resolved after 15 days (Table 3).

Discussion

Influenza is one of the most common infectious diseases that in seasonal flu epidemics affect different people in all age groups. Infections caused by the virus can be very serious, and lead to severe post-influenza complications, including primary influenza pneumonia or secondary bacterial pneumonia. Complications of influenza are more common, especially in the elderly and in patients with malignancies due to deficiencies in humoral and cellular immunity.

Factors involved in the development of an effective immune response to the vaccine include baseline immunoglobulin IgG levels, immune status, the presence of active disease, the previous or current treatment, age, and the previous vaccines (6). In this study, which evaluated the value of the flu vaccination in patients with various malignancies during the Covid-19 pandemic, patients were divided into two categories: solid cancer and hematological cancer.

There is always this pessimism in the medical community about receiving the flu vaccine in patients with hematologic cancer due to changes in the immune system induced by the disease or following chemotherapy. This issue has become more pronounced in the coronavirus pandemic due to the potential for vaccine ineffectiveness and its potentially harmful side effects. However, it should not be overlooked that infections are the leading cause of death in patients with hematologic cancers (7). Patients with hematologic cancer in this study included multiple myeloma, lymphoma, and Hodgkin's disease. There have been recommendations in previous reports about the requisiteness to administer the flu vaccine to this group of patients. Rapezzi et al. Examined the effects of influenza vaccine in 34 patients with hematological cancer during the flu season (October to April). The results of their studies showed that there were no adverse reactions after vaccination in these patients and seroprotection and seroconversion were higher than the standard of the European Agency for

the Evaluation of Medicinal Products. Only one patient had the flu after a follow-up. They suggested that the flu vaccine could be well tolerated in this group of patients and was not contraindicated (6). In five vaccinated hematological cancer patients, despite receiving *rituximab*, no adverse effects of the vaccine reported. However, previous studies have reported ineffective vaccine immunogenicity in this group of patients. Yri et al. investigated humoral responses to influenza vaccination in lymphoma patients with rituximab monotherapy or combination therapy. They suggested that there is no protective immunity from the vaccine in any case against influenza A (H1N1) 2009 (swine flu virus). They concluded that these patients may not respond well enough not only to the flu vaccine but also to other common vaccines (8).

Among those who were vaccinated was a cancer patient with a history of liver transplantation who did not experience the side effects of the vaccine after one month of follow-up. The safety and immunogenicity of influenza vaccination in transplant recipients have been previously evaluated (9, 10). Pérez-Romero et al., in a prospective cohort study in 798 solid organ transplant recipients, investigated the safety and immunogenicity of flu vaccination 6 months and more after transplantation. They resulted that influenza vaccination within the first 6 months after transplantation is as safe and immunogenic as vaccination thereafter. so they recommended the administration of flu vaccination as soon as 1 month after transplantation (11).

Previous findings also suggest that influenza vaccine in high-risk groups such as the heart (12), kidney (13), and rheumatoid arthritis (14) patients are a cost-effective preventative measure that improves survival and reduces the incidence of underlying disease in high-risk populations.

One of the cancer patients became infected with coronavirus after vaccination, which, of course, was due to the spread of the disease through caregivers. The incidence of coronavirus in this person who had previously received the flu vaccine was mild and without severe pulmonary symptoms. Although, more detailed research is needed to evaluate the effect of the influenza vaccine on the incidence of coronavirus disease. According to the recommendations we had to this group of patients in using masks and gloves and maintaining a safe distance to prevent coronavirus disease, the incidence in these patients was very low, and the incidence occurred due to non-compliance with the recommended cases.

Our study revealed that vaccination in cancer patients during the coronavirus pandemic did not increase the risk of this disease and did not induce severe vaccine-induced complications in patients. Generally, cancer patients are recommended to receive the flu vaccine annually during the pandemic and after the end of this pandemic, usually during the flu epidemic season to reduce mortality.

Conflicts of interest

The authors have no conflict of interest to declare.

Author's Contribution

All authors contributed to the design and execution of the study. All authors participated in article drafting and critical revision. All authors read and approved the final version of the manuscript.

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Table 1 Frequency, percentage, and Mean \pm Standard deviation age of eligible cancer patients for getting influenza vaccine (vaccination from October 1 to 15, 2020)

type	Frequency	Percent	mean	SD	Min	Max
Biliary Tract	7	2.4	54.43	7.5	43	63
Bladder	3	1.0	61	2.000	59	63
Breast	107	37.2	48.34	11.6	27	74
Cervix	2	0.7	46	8.5	40	52
Gastrointestinal	85	29.5	56.28	11.5	26	76
Glioblastoma Multiform	4	1.4	51.25	2.9	49	55
Hematological	29	10.1	51.66	16.5	18	78
Lung	14	4.9	58	7.5	43	66
Melanoma	2	0.7	41	4.2	38	44
Metastasis of unknown origin	2	0.7	55.5	6.4	51	60
Nasopharyngeal Carcinoma	2	0.7	34	2.8	32	36
Osteosarcoma	2	0.7	33	1.4	32	34
Ovarian	6	2.1	49	12.3	35	64
Pancreas	6	2.1	55.33	8.4	48	66
Salivary and Parotid	2	0.7	59	24	42	76
Sarcoma	2	0.7	42	0.0	42	42
Testis and Prostate	4	1.4	58	21.1	29	79
Uterine	3	1.0	54.33	7.0	47	61
Other*	6	2.1	46	11.5	31	66
Total	288	100.0	51.92	12.46	18	79

* Other cancers include: Brain, Desmoids, Hepatocellular carcinoma, Peri-ampullary, Squamous Cell Carcinoma, and Thymoma

Table 2 Frequency and percentage of eligible cancer patients for getting influenza vaccine in terms of Covid-19 disease or history of that, comorbidity, and the adverse effect of vaccination based on demographic variables and disease stage in different types of cancer (vaccination from October 1 to 15, 2020)

variable	categorical	Covid-19		Comorbidity		The adverse effect of vaccination		total
		yes	No	yes	No	yes	No	
gender	male	3	109	2	110	1	111	112
		2.7%	97.3%	1.8%	98.2%	0.9%	99.1%	
	female	2	174	2	174	1	175	176
		1.1%	98.9%	1.1%	98.9%	0.6%	99.4%	
Age group	< 40	1	48	1	48	0	49	49
		2.0%	98.0%	2.0%	98.0%	0.0%	100.0%	
	40 - 59	3	150	2	151	2	151	153
		2.0%	98.0%	1.3%	98.7%	1.3%	98.7%	
	≥ 60	1	85	1	85	0	86	86
		1.2%	98.8%	1.2%	98.8%	0.0%	100.0%	
Stage	II	0	51	0	51	0	51	51
		0.0%	100.0%	0.0%	100.0%	0.0%	100.0%	
	III	1	77	2	76	0	78	78
		1.3%	98.7%	2.6%	97.4%	0.0%	100.0%	
	IV	2	86	1	87	2	86	88
		2.3%	97.7%	1.1%	98.9%	2.3%	97.7%	
	Relapsed	0	33	0	33	0	33	33
		0.0%	100.0%	0.0%	100.0%	0.0%	100.0%	
	unknown	2	36	1	37	0	38	38
		5.3%	94.7%	2.6%	97.4%	0.0%	100.0%	
Rituximab	yes	0	5	0	5	0	5	5
		0.0%	100.0%	0.0%	100.0%	0.0%	100.0%	
	no	5	278	4	279	2	281	283
		1.8%	98.2%	1.4%	98.6%	0.7%	99.3%	
Total		5*	283	4**	284	2***	287	288

* Four patients before the vaccination and one (a 48-year-old woman with biliary tract cancer) after the vaccination got COVID-19.

** Patients with comorbidities other than cancer (including liver transplant, congestive heart failure, rheumatoid arthritis, and renal failure)

*** Two patients with colon and breast cancer (grade IV), one of them with a history of Covid-19 before vaccination, four and ten days after vaccination had experienced side effects of vaccination (bone pain, fatigue, and runny nose), respectively.

Table 3 Frequency and percentage of eligible cancer patients for getting influenza vaccine in terms of Covid-19 disease or history of that, comorbidity, and the adverse effect of vaccination based on cancer types (vaccination from October 1 to 15, 2020)

Type	Covid-19		Comorbidity		The adverse effect of vaccination		total
	yes	No	yes	No	yes	No	
Biliary Tract	1	6	0	7	0	7	7
	14.3 %	85.7%	0.0%	100.0%	0.0%	100.0 %	
Bladder	0	3	0	3	0	3	3
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0 %	
Breast	0	107	1	106	1	106	107
	0.0%	100.0%	0.9%	99.1%	0.9%	99.1%	
Cervix	0	2	1	1	0	2	2
	0.0%	100.0%	50.0%	50.0%	0.0%	100.0 %	
Gastrointestinal	3	82	1	84	1	84	85
	3.5%	96.5%	1.2%	98.8%	1.2%	98.8%	
Glioblastoma Multiform	0	4	0	4	0	4	4
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0 %	
Hematological	1	28	0	29	0	29	29
	3.4%	96.6%	0.0%	100.0%	0.0%	100.0 %	
Lung	0	14	0	14	0	14	14
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0 %	
Melanoma	0	2	0	2	0	2	2
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0 %	
Metastasis of unknown origin	0	2	0	2	0	2	2
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0 %	
Nasopharyngeal Carcinoma	0	2	0	2	0	2	2
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0 %	
Osteosarcoma	0	2	0	2	0	2	2
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0 %	
Ovarian	0	6	0	6	0	6	6
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0 %	
Pancreas	0	6	0	6	0	6	6
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0 %	
Salivary and Parotid	0	2	0	2	0	2	2
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0 %	
Sarcoma	0	2	0	2	0	2	2
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0 %	

Testis and Prostate	0	4	0	4	0	4	4
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%	
Uterine	0	3	0	3	0	3	3
	0.0%	100.0%	0.0%	100.0%	0.0%	100.0%	
Other	0	6	1	5	0	6	6
	0.0%	100.0%	16.7%	83.3%	0.0%	100.0%	
Total	5	283	4	284	2	286	288

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