



Value of influenza vaccines in cancer patients during the coronavirus (COVID-19) pandemic: a cross-sectional study

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Abstract

Background 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 study, the value of influenza vaccination in the cancer population was investigated.

Methods In a cross-sectional study, 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 November 15, 2020 were investigated. The most side effects that were followed were fever, runny nose, bone pain, and life-threatening or persistent adverse effects.

Results From a total of 288 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. 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.

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

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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.

This cross-sectional descriptive study has been organized according to the STROBE checklist. 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 the following up clinical signs every week for one month. The types of cancers in our study and the treatments used for each are presented in Table 1. Those patients who were vaccinated (one 0.5 ml dose) from October 1 to November 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 2).

However, most patients with hematologic malignancy were not candidates for the vaccine due to the type of treatment they received, such as *rituximab*. Since this study was performed in a single clinical center and on a limited number of patients with various types of cancers, it can be said that maybe there is a selection bias in this study.

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 2-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, and life-threatening or persistent adverse effects.

Data were analyzed using the 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%) (Tables 1 and 2). 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 3). Indeed, 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 before receiving the vaccine. These patients were well after receiving the flu vaccine. One of the patients with biliary tract cancer, after receiving the flu vaccine, became infected with coronavirus through medical staff; however, he returned to the normal feeling after a few days. This patient had a dry cough, shortness of breath, and saturation O_2 90%, and according to the CT scan report, the pulmonary involvement was not severe. Reverse transcription-polymerase chain reaction (RT-PCR), besides the computerized tomography (CT) scan, was the main technique in diagnosing COVID-19. One case of patients with colon cancer (stage IV) and a history of COVID-19 suffered from the vaccine's side effects such as bone pain, fatigue, diarrhea, and runny nose. Besides, a patient with metastatic breast cancer (stage IV) had significant side effects 4 days after receiving the vaccine, which resolved after 15 days. This patient had a fever, shivering, myalgia, headache, severe fatigue, and sweating (Table 4).

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

Table 1 The chemotherapy program for cancer patients eligible to receive the flu vaccine during the COVID-19 pandemic

Cancer types	Chemotherapy
Amyloidosis	Melph/PRD
Biliary tract	Gem/Cis/5FU or Capaci/Erlo
Bladder	Gem/Cis
Brain	PVC
Breast	TEC or Gem/Nav or Herceptin or Capaci/Nav or Everolimus
Cervix	Tax/Carb/Av or Tax/Doxo/Cis
CLL	Chlo/PRD
Colon	Folfox/Av or Capaci/OX or Folfiri/Av or Folfiri/Erb or Regorafenib
Desmoid tumor	Doxo
SCC	Tax/Cis/5FU
Esophagus	Tax/Cis/5FU
Gastric	Folfiri/Carb or Tax/Cis/5FU
GBM	PVC
HCC	Nexavar
HD	ABVD or Benda/Gem
Lung	Tax/Carb or Etop/Cis
Lymphoma	Rituximab
Melanoma	DTIC/INF-gamma
MM	CVAD-Th or Melph/PRD or lenalidomide
NPC	Tax/Cis/5FU/ER
Osteosarcoma	Tax/Gem
Ovarian	Tax/Carb or Tax/Carb/Av or Caelyx/Car
Pancreas	Gem/Cis/5FU
Parotid	Tax/Cis/5FU
Periampullary	Gem/Cis/F
Prostate	Docetaxel (Taxotere)
Rectum	Folfox/Av
Salivary gland	Tax/Cis/5FU
Small intestine	Folfiri/Av
Uterine	Tax/Doxo/Cis

Melph melphalan; *PRD* prednisone; *Gem* gemcitabine; *Cis* cisplatin; *Capaci* capecitabine; *Nav* Navelbine; *TEC* taxotere-epirubicin-cyclophosphamide; *PVC* procarbazine-lomustine-vincristine; *Carb* carboplatin; *Av* Avastin (bevacizumab); *Tax* paclitaxel; *Doxo* doxorubicin; *Chlo* chlorambucil; *Folfox* folinic acid (leucovorin)-fluorouracil (5FU)-oxaliplatin (Eloxatin); *5FU* 5-fluorouracil; *Folfiri* leucovorin calcium (folinic acid)-fluorouracil-irinotecan hydrochloride; *Erb* erbitux (cetuximab); *ABVD* adriamycin (doxorubicin)-bleomycin-vinblastine-dacarbazine; *Benda* bendamustine; *Etop* etoposide; *DTIC* dacarbazine; *INF* interferon; *CVAD-Th* cyclophosphamide, vincristine, doxorubicin, dexamethasone-thalidomide; *HD* Hodgkin's disease; *MM* multiple myeloma; *HCC* hepatic cell carcinoma; *SCC* squamous cell carcinoma; *CLL* chronic lymphocytic leukemia; *GBM* glioblastoma multiform

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 the influenza vaccine in 34 patients with hematological cancer during the flu season (October to April). The results of their studies showed

Table 2 Frequency, percentage, and mean \pm standard deviation age of eligible cancer patients for getting influenza vaccine (vaccination from October 1 to November 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, periampullary, squamous cell carcinoma, and thymoma

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 demographic variables and disease stage in different types of cancer (vaccination from October 1 to November 15, 2020)

Variable	Categorical	COVID-19		Comorbidity		The adverse effect of vaccination		Total
		Yes	No	Yes	No	Yes	No	
Gender	Male	3 2.7%	109 97.3%	2 1.8%	110 98.2%	1 0.9%	111 99.1%	112
	Female	2 1.1%	174 98.9%	2 1.1%	174 98.9%	1 0.6%	175 99.4%	
Age group	< 40	1 2.0%	48 98.0%	1 2.0%	48 98.0%	0 0.0%	49 100.0%	49
	40-59	3 2.0%	150 98.0%	2 1.3%	151 98.7%	2 1.3%	151 98.7%	
	\geq 60	1 1.2%	85 98.8%	1 1.2%	85 98.8%	0 0.0%	86 100.0%	
Stage	II	0 0.0%	51 100.0%	0 0.0%	51 100.0%	0 0.0%	51 100.0%	51
	III	1 1.3%	77 98.7%	2 2.6%	76 97.4%	0 0.0%	78 100.0%	
	IV	2 2.3%	86 97.7%	1 1.1%	87 98.9%	2 2.3%	86 97.7%	
	Relapsed	0 0.0%	33 100.0%	0 0.0%	33 100.0%	0 0.0%	33 100.0%	
	Unknown	2 5.3%	36 94.7%	1 2.6%	37 97.4%	0 0.0%	38 100.0%	
Rituximab	Yes	0 0.0%	5 100.0%	0 0.0%	5 100.0%	0 0.0%	5 100.0%	5
	No	5 1.8%	278 98.2%	4 1.4%	279 98.6%	2 0.7%	281 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, 4 and 10 days after vaccination had experienced side effects of vaccination (bone pain, fatigue, and runny nose), respectively

Table 4 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 November 15, 2020)

Type	COVID-19		Comorbidity		The adverse effect of vaccination		Total
	Yes	No	Yes	No	Yes	No	
Biliary tract	1 14.3%	6 85.7%	0 0.0%	7 100.0%	0 0.0%	7 100.0%	7
Bladder	0 0.0%	3 100.0%	0 0.0%	3 100.0%	0 0.0%	3 100.0%	3
Breast	0 0.0%	107 100.0%	1 0.9%	106 99.1%	1 0.9%	106 99.1%	107
Cervix	0 0.0%	2 100.0%	1 50.0%	1 50.0%	0 0.0%	2 100.0%	2
Gastrointestinal	3 3.5%	82 96.5%	1 1.2%	84 98.8%	1 1.2%	84 98.8%	85
Glioblastoma multiform	0 0.0%	4 100.0%	0 0.0%	4 100.0%	0 0.0%	4 100.0%	4
Hematological	1 3.4%	28 96.6%	0 0.0%	29 100.0%	0 0.0%	29 100.0%	29
Lung	0 0.0%	14 100.0%	0 0.0%	14 100.0%	0 0.0%	14 100.0%	14
Melanoma	0 0.0%	2 100.0%	0 0.0%	2 100.0%	0 0.0%	2 100.0%	2
Metastasis of unknown origin	0 0.0%	2 100.0%	0 0.0%	2 100.0%	0 0.0%	2 100.0%	2
Nasopharyngeal carcinoma	0 0.0%	2 100.0%	0 0.0%	2 100.0%	0 0.0%	2 100.0%	2
Osteosarcoma	0 0.0%	2 100.0%	0 0.0%	2 100.0%	0 0.0%	2 100.0%	2
Ovarian	0 0.0%	6 100.0%	0 0.0%	6 100.0%	0 0.0%	6 100.0%	6
Pancreas	0 0.0%	6 100.0%	0 0.0%	6 100.0%	0 0.0%	6 100.0%	6
Salivary and parotid	0 0.0%	2 100.0%	0 0.0%	2 100.0%	0 0.0%	2 100.0%	2
Sarcoma	0 0.0%	2 100.0%	0 0.0%	2 100.0%	0 0.0%	2 100.0%	2
Testis and prostate	0 0.0%	4 100.0%	0 0.0%	4 100.0%	0 0.0%	4 100.0%	4
Uterine	0 0.0%	3 100.0%	0 0.0%	3 100.0%	0 0.0%	3 100.0%	3
Other	0 0.0%	6 100.0%	1 16.7%	5 83.3%	0 0.0%	6 100.0%	6
Total	5	283	4	284	2	286	288

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 were 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 1 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 a month after transplantation [11].

Previous findings also suggest that the influenza vaccine in high-risk groups such as the heart [12], kidney [13], and rheumatoid arthritis [14] patients is 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. This person, who had previously received the flu vaccine, developed a mild form of the Covid-19 disease without severe pulmonary symptoms. It should be noted, however, that more detailed research is needed to evaluate the effect of the influenza vaccine on susceptibility to Covid-19. According to the recommendations [15] 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.

Study limitations

In this study, all patients had a type of cancer and were under chemotherapy. Because this study was performed in a single clinical center, the sample size in each type of cancer cannot be generalized to all cancer patients. Therefore, there may be a selection bias in this study.

On the other hand, our study population did not have the same frequency distribution in cancer subgroups and cancer stages, so the response and non-response to vaccine side effects cannot be attributed to a particular type of cancer or in a particular stage. The frequency of people with breast cancer and gastrointestinal cancer was more than other cancers, so the chances of response in these types of cancer were higher.

Although there were no side effects in people with a history of COVID-19 after flu vaccination, it cannot be concluded that receiving the flu vaccine in cancer patients with a history of COVID-19 had no side effects. To reach this conclusion,

more sample size in each type of cancer and from several clinical centers is needed.

Conclusion

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.

Author's contribution Aznab M: concepts, design, definition of intellectual content, clinical studies, manuscript preparation, manuscript editing, manuscript review, data acquisition, guarantor; Eskandari Roozbahani N: concepts, design, literature search, data acquisition, data analysis, manuscript preparation, manuscript editing, manuscript review; Moazen H: literature search, data acquisition, statistical analysis, manuscript preparation, manuscript review.

Availability of data and material No additional data are available.

Code availability N/A.

Declarations

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

Consent to participate Verbal informed consent was obtained before the interview.

Consent for publication The participant has consented to the submission of the case report in the journal.

Competing interests The authors declare no competing interests.

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