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RESEARCH PAPER

Immunogenicity of trivalent influenza vaccine in patients with lung cancer undergoing anticancer chemotherapy

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ABSTRACT

Lung cancer is a leading cause of cancer-related death, and patients with lung cancer are a priority group for influenza vaccination. However, few studies have assessed the immunogenicity of the influenza vaccine in these patients. Here, we performed a prospective study to evaluate the immunogenicity of the influenza vaccine in patients with lung cancer undergoing anticancer chemotherapy. Twenty-five patients with lung cancer undergoing anticancer chemotherapy and 26 patients with chronic obstructive pulmonary disease (COPD) as controls were enrolled. A trivalent influenza vaccine containing inactivated A/California/7/2009 (H1N1) pdm09, A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012 was administered as a single subcutaneous injection. Serum samples were collected before vaccination, and at 4–6 weeks after vaccination. Levels of serum antibody to hemagglutinin were measured. Among patients with lung cancer, the seroprotection rate (postvaccination titer > 1:40) was 84% for both A(H1N1) and A(H3N2), similar to the levels observed in patients with COPD. However, the seroprotection rate for the B strain was significantly lower in patients with lung cancer than in patients with COPD (64% versus 92%). Even after adjustment for potential confounders, patients with lung cancer had a significantly lower odds ratio for seroprotection against the B strain than patients with COPD. Moreover, in patients with lung cancer, those receiving the platinum doublet treatment tended to exhibit a lower seroprotection rate than those receiving a single agent. Thus, patients with lung cancer undergoing anticancer chemotherapy showed acceptable immune responses to a trivalent influenza vaccine, supporting the recommendation for annual influenza vaccination in these patients.

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Introduction

Patients with cancer undergoing systemic chemotherapy have a significant risk of morbidity and mortality from influenza infection.[1,2] According to a previous report,[1] the mortality rate for influenza infection is approximately 9% among patients with cancer. In addition, influenza infection and influenza-related complications often prevent consecutive courses of chemotherapy and worsen the prognosis of these patients.[1,3,4] Therefore, annual influenza vaccination is recommended in patients with cancer for the prevention of severe influenza or related bacterial infections.[2,5,6] Despite this recommendation, prior studies have reported low influenza vaccination rates among patients receiving chemotherapy for cancer.[7,8] The main reasons for the absence of vaccination include lack of recommendation by the treating physician (72%), fear of side effects (33%), and concerns regarding vaccination efficacy (10%).[7] Moreover, information concerning influenza vaccine efficacy, safety, and optimal timing in patients with cancer is limited.[3] However, the immunogenicity of influenza vaccination in cancer patients has been reported in several studies.[3] The reported seroprotection rates (sPs; postvaccination titer > 1:40) of the inactivated influenza vaccine in patients with solid cancers ranges from 38%–78%.[9-11] The intensity and type of chemotherapy and the timing of vaccination in the course of chemotherapy influence the immunogenicity of influenza vaccination.[3]

Lung cancer is the leading cause of cancer-related death among men and women.[12] Owing to the high incidence of lung cancer worldwide, influenza vaccination for this group of patients is crucial. However, to our knowledge, only one study, performed in 1999, has assessed the immunogenicity of influenza vaccine in patients with lung cancer.[9] In addition, in the last few years, the intensity of anticancer chemotherapy has changed with the development and introduction of new drugs such as platinum agents, third-generation drugs, pemetrexed, and bevacizumab.[13]

Therefore, in this study, we aimed to evaluate the immunogenicity of the influenza vaccine in patients with lung cancer undergoing anticancer chemotherapy compared with that in patients with chronic obstructive disease (COPD) as an immunocompetent control. The study subjects were recruited from the Kameda Medical Center, a tertiary care and teaching hospital, which has 925 inpatient beds, 34 clinical departments, and

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3000 medical staffs. The Kameda Medical Center covers the southern area of Chiba, Japan, which has a population of ~1,000,000. Since immunoresponses are influenced by prevaccination titers, which are related to previous virus exposure (through infection or vaccination), we used logistic regression to analyze models that include potential confounders, including prevaccination titer, as explanatory variables.

Results

A total of 25 patients with lung cancer and 27 patients with COPD were eligible for this study. All patients received one dose of the trivalent influenza vaccine between November and December 2013. Serum samples at 4–6 weeks after vaccination were collected from 25 patients with lung cancer and 26 patients with COPD. One patient with COPD showed a mild rash within 48 h after vaccination, and no other severe adverse events occurred in any of the patients with lung cancer or COPD. During the study period, no subjects reported laboratory-confirmed influenza or influenza-like illness (defined by acute febrile illness [temperature > 38.0°C] with one or more respiratory symptoms [nasal discharge, sore throat, or cough]).

The characteristics of the 51 patients included in the immunogenicity analyses are shown in Table 1. The mean age was 69.4 years, and 41 patients (80.4%) were men. The proportions of patients with pretiter levels of 1:10 or more ranged from 48%–68% in patients with lung cancer and from 69%–88% in patients with COPD. For the A/California/7/2009 (H1N1) pdm09 strain, the percentage of patients with pretiter levels of 1:10 or more was significantly higher in patients with COPD than that in patients with lung cancer. Adenocarcinoma was the most common histological type in patients with lung cancer (40%). Fifteen (60%) patients received chemotherapy with platinum doublet treatment, and 10 (40%) patients received chemotherapy with a single agent.

Table 2 shows the immune responses to the trivalent influenza vaccination among patients with lung cancer or COPD. Patients with lung cancer showed significantly lower geometric mean titers (GMTs) for A/California/7/2009 (H1N1) pdm09 before vaccination than patients with COPD. In the other 2 strains, patients with lung cancer tended to show lower GMTs before vaccination than patients with COPD did. In all strains, GMTs reached the protection levels (≥1:40), and the mean fold rise (MFR) values were over 2.0 fold. The sPs and seroresponse rates (sRs) in patients with lung cancer were 64%–84% and 60%–72%, respectively. In the A/California/7/2009 (H1N1) pdm09 and A/Texas/50/2012 (H3N2) strains, there were no significant differences in sPs between patients with lung cancer and those with COPD. However, the sP of B/Massachusetts/02/2012 in patients with lung cancer was significantly lower than that in patients with COPD (64% vs. 92%, respectively; $p = 0.019$). In all strains, sRs were not significantly different between patients with lung cancer and patients with COPD.

Table 3 shows the odds ratios (ORs) for sRs after trivalent influenza vaccination in patients with lung cancer compared with those in patients with COPD. In all strains, there were no significant reductions in ORs in patients with lung cancer compared with that in patients with COPD, in both the crude analysis and multivariate analysis.

Table 4 shows ORs for seroconversion reats (sCs) after trivalent influenza vaccination in patients with lung cancer compared with those in patients with COPD. For all strains, based on ORs, there were no significant differences between patients with lung cancer and patients with COPD in the multivariate analysis.

Table 5 shows ORs for sPs after trivalent influenza vaccination in patients with lung cancer compared with those in patients with COPD. In B/Massachusetts/02/2012, patients with lung cancer had a significantly lower OR for sP than patients with COPD ($p = 0.028$) in the multivariate analysis. For the other 2 strains, the ORs for sPs were not significantly different between the 2 patient groups.

Table 6 shows the immune responses to trivalent influenza vaccination among patients with lung cancer undergoing anticancer chemotherapy. For A/Texas/50/2012(H3N2), the MFR was 3.6 in patients receiving platinum doublet treatment; this was significantly lower than that in patients receiving treatment with a single agent (11.3; $p = 0.049$). The sPs were lower in patients receiving platinum doublet treatment, although these differences were not significant, for A/California/7/2009 (H1N1) pdm09 (platinum doublet treatment versus single agent treatment: 73% vs. 100%; $p = 0.125$), A/Texas/50/2012 (H3N2) (platinum doublet treatment versus single agent treatment: 73% vs. 100%; $p = 0.125$), and B/Massachusetts/02/2012 (platinum doublet treatment versus single agent treatment: 60% vs. 70%; $p = 0.691$).

Discussion

In this study, we showed that influenza vaccination induced sufficient immune responses in both patients with COPD and those with lung cancer. The immunity after vaccination satisfied the international licensing criteria of the European Agency for the Evaluation of Medical Products and the US Food and Drug Administration.[14,15] For the A/California/7/2009 (H1N1) pdm09 and A/Texas/50/2012 (H3N2) strains, there were no significant differences in the ORs for sP, sR, or sC between patients with COPD and those with lung cancer in the multivariate analysis. However, the OR for the sP of B/Massachusetts/02/2012 was significantly reduced in patients with lung cancer in the multivariate analysis. In addition, the sP, sR, and sC tended to be lower in patients receiving platinum doublet treatment than in patients receiving single agent treatment. Thus, platinum doublet chemotherapy is considered a high-intensity treatment and may suppress the ability of the immune system to make anti-influenza antibodies.

Oncology patients are heterogeneous, and the immunogenicity of the influenza vaccine in patients with cancer differs depending on the type of cancer and the intensity of chemotherapy.[3,16] Some studies have shown that immunization with the influenza vaccine has no benefit in providing adequate seroconversion, particularly in patients with hematological diseases such as lymphomas and multiple myeloma.[17-20] Nevertheless, other studies examining the immunogenicity of vaccination in hematological disease have reported adequate immunoresponses.[21,22] In addition, positive data have been obtained in the majority of studies assessing the immunogenicity of the influenza vaccine in

Table 1. Characteristics of patients with lung cancer or COPD.

Variables		Lung cancer (N = 25)	COPD (N = 26)	*P* value*
Age, years (mean ± SD)		68.0 ± 6.3	70.7 ± 7.4	0.157
Male		18 (72%)	23 (88%)	0.173
Prevaccination titer				
A/California/7/2009(H1N1)pdm09				
	<1:10	13 (52%)	6 (23%)	0.045
	≥1:10	12 (48%)	20 (77%)	
A/Texas/50/2012(H3N2)				
	<1:10	8 (32%)	3 (12%)	0.098
	≥1:10	17 (68%)	23 (88%)	
B/Massachusetts/02/2012				
	<1:10	11 (44%)	8 (30%)	0.393
	≥1:10	14 (56%)	18 (69%)	
Stage of COPD				
GOLD stage 1			7 (27%)	
GOLD stage 2			11 (42%)	
GOLD stage 3			6 (23%)	
GOLD stage 4			2 (8%)	
Histological type of lung cancers				
Adenocarcinoma		10 (40%)		
Squamous cell carcinoma		6 (24%)		
Small cell carcinoma		8 (32%)		
Others		1 (4%)		
Tumor stage				
Stage 1		1 (4%)		
Stage 3		4 (16%)		
Stage 4		17 (68%)		
Recurrence after surgery		2 (8%)		
Recurrence after stereotactic radiotherapy		1 (4%)		
Recent chemotherapy duration of subjects on influenza vaccination (months)				
0–2		10 (40%)		
3–5		6 (24%)		
6–8		1 (4%)		
9–11		2 (8%)		
≥12		6 (24%)		
Chemotherapy in patients with lung cancer		25 (100%)		
Platinum doublet		15 (60%)		
	CDDP + DOC	1 (4%)		
	CDDP + VP-16	2 (8%)		
	CBDCA + PTX	3 (12%)		
	CBDCA + PEM	3 (12%)		
	CBDCA + nab-PTX	2 (8%)		
	CBDCA + TS1	1 (4%)		
	CBDCA + VP-16	3 (12%)		
Single agent		10 (40%)		
	DOC	3 (12%)		
	AMR	3 (12%)		
	PEM	1 (4%)		
	GEM	1 (4%)		
	VNR	1 (4%)		
	PTX	1 (4%)		

Data are expressed as number (%) of patients, unless otherwise indicated.
COPD: chronic obstructive pulmonary disease.
GOLD: Global Initiative for Chronic Obstructive Lung Disease.
CDDP: cisplatin; DOX: docetaxel; VP-16: etoposide; PTX: paclitaxel; PEM: pemetrexed; Nab-PTX: nab-paclitaxel; TS1: tegafur, gimeracil, oteracil potassium; AMR: amrubicin; GEM: gemcitabine; VNR: vinorelbine.
SD: standard deviation.
*P values were calculated by Fisher's exact or student's t tests.

patients with solid tumors such as breast cancer, colorectal cancer, and lung cancer.[9,10,23,24] Although the observed immunogenicity in patients with solid tumors undergoing chemotherapy has been shown to reach protective levels,[9-11,23-25] some reports have shown that the immunogenicity induced by vaccination is lower than that in immunocompetent controls.[10,23] A previous study assessing the immunogenicity of the influenza vaccine in patients with lung cancer showed an sP of 78% (postvaccination titer > 1:40), similar to the seroprotection level of 64%–84% in our study.[9]

In the present study, the sP of B/Massachusetts/02/2012 in patients with lung cancer was 64%, which was significantly lower than that for patients with COPD and was relatively low in comparison with that of the other 2 strains in patients with lung cancer. A previous report showed increased sensitivity and reduced specificity of hemagglutination inhibition tests with an ether-treated influenza B strain.[26] In our study, none of

Table 2. Immune responses to the trivalent influenza vaccine in patients with lung cancer or COPD.

	Geometric mean titer[a]		Mean fold rise[a]	after vaccination[b]		
	Before vaccination (S0)	after vaccination (S1)	S1/S0	Seroprotection rate (sP) (≥1:40): n (%)	Seroresponse rate (sR) (≥4 fold-rise): n (%)	Seroconversion rate (sC) n (%)
A/California/7/2009 (H1N1)pdm09						
Lung cancer	11	105	9.4	21 (84)	18 (72)	18 (72)
COPD	25	123	5.0	21 (81)	13 (50)	11 (42)
	($P = 0.011$)	($P = 0.923$)	($P = 0.132$)	($P = 1.000$)	($P = 0.153$)	($P = 0.048$)
A/Texas/50/2012 (H3N2)						
Lung cancer	19	112	5.7	21 (84)	16 (64)	14 (56)
COPD	37	173	4.7	25 (96)	13 (50)	13 (50)
	($P = 0.079$)	($P = 0.467$)	($P = 0.445$)	($P = 0.191$)	($P = 0.400$)	($P = 0.781$)
B/Massachusetts/02/ 2012						
Lung cancer	13	54	4.2	16 (64)	15 (60)	12 (48)
COPD	22	91	4.2	24 (92)	13 (50)	12 (46)
	($P = 0.141$)	($P = 0.271$)	($P = 0.931$)	($P = 0.019$)	($P = 0.577$)	($P = 1.000$)

[a]Wilcoxon rank-sum test was performed for intercategory comparisons.
[b]Seroprotection rates, seroresponse rates, and seroconversion rates were compared between groups by Fisher's exact test.

the 3 strains was treated with ether. Hence, we believe that the differences in sPs among strains were not derived from variations in methodology. Concerning this relatively poor immune response to B/Massachusetts/02/2012 in patients with lung cancer, our results were similar to those of a prior study, in which the immunogenicity of an inactive quadrivalent influenza vaccine containing the B/Massachusetts/02/2012 strain was evaluated.[27] It is possible that pre-existing immunity to B strains other than B/Massachusetts/02/2012 negatively affected the immune response to the B/Massachusetts/02/2012 strain; this phenomenon is called original antigenic sin.[28,29] For example, a previous study assessing the prime-boost responses following a change in the 2 B lineages (B/Yamagata and B/Victoria) reported the influence of original antigenic sin on responses to B strains; repeated administration of the annual trivalent influenza vaccine containing the B/Victoria lineage antigen strongly recalled antibodies to the B/Yamagata antigen after the first exposure, but elicited lower B/Victoria responses.[30] In Japan, a mixed epidemic of B/Victoria and B/Yamagata was observed during the 2011/2012 and 2012/2013 seasons.[31] During these seasons, some participants in our study could have been sensitized to the B/Victoria or B/Yamagata strain, thereby decreasing immunogenicity to B/Massachusetts/02/2012 (B/Yamagata lineage) owing to the influence of original antigenic sin on responses to B strains. Moreover, the lower prevaccination antibody titer in patients with lung cancer may explain the decreased sP. In the present study, most of the patients with lung cancer had received repetitive chemotherapy at the time of vaccination, potentially strengthening the lower GMTs before vaccination owing to the immunosuppression caused by chemotherapy.

In this study, we chose patients with COPD as the immunocompetent control group because they are also a priority group for influenza vaccination,[32,33] and are considered immunocompetent compared to patients with cancer undergoing chemotherapy. However, whether patients with COPD are suitable as a control group may be controversial because there is insufficient high-quality evidence on current influenza vaccine regimens for patients with COPD.[34] In a prior study, patients with COPD and healthy controls obtained seroprotective levels of antibodies after influenza vaccination, although the sR seemed to be lower in patients with COPD than in healthy participants, because of the higher prevaccination titer in patients with COPD.[35] In addition, our study showed that the sPs among patients with COPD reached 81%–96% after vaccination. Thus, the patients with COPD in our study appeared to be appropriate as a control group.

Our study has several limitations. First, we had a relatively small sample size. Enrollment of patients was restricted by the

Table 3. Odds ratios for seroresponse rates at after trivalent influenza vaccination in patients with lung cancer or COPD.

	Seroresponse rate (sR) (≥4 fold-rise): n (%)	Crude analysis		Multivariate analysis*	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
A/California/7/2009(H1N1)pdm09					
Lung cancer	18 (72)	2.52 (0.70–9.79)	0.153	1.29 (0.27–6.29)	0.749
COPD	13 (50)	1.00 (ref.)		1.00 (ref.)	
A/Texas/50/2012(H3N2)					
Lung cancer	16 (64)	1.76 (0.51–6.35)	0.400	1.11 (0.30–4.15)	0.872
COPD	13 (50)	1.00 (ref.)		1.00 (ref.)	
B/Massachusetts/02/2012					
Lung cancer	15 (60)	1.49 (0.43–5.25)	0.577	1.02 (0.28–3.78)	0.975
COPD	13 (50)	1.00 (ref.)		1.00 (ref.)	

*Adjusted for age, gender, and prevaccination titer.

Table 4. Odds ratios for seroconversion rates after trivalent influenza vaccination in patients with lung cancer or COPD.

	Seroconversion rate (sC): n (%)	Crude analysis		Multivariate analysis*	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
A/California/7/2009(H1N1)pdm09					
Lung cancer	18 (72)	3.42 (0.95–13.4)	0.048	2.48 (0.62–9.99)	0.200
COPD	11 (42)	1.00 (ref.)		1.00 (ref.)	
A/Texas/50/2012(H3N2)					
Lung cancer	14 (56)	1.27 (0.37–4.41)	0.781	0.88 (0.25–3.1)	0.847
COPD	13 (50)	1.00 (ref.)		1.00 (ref.)	
B/Massachusetts/02/2012					
Lung cancer	12 (48)	1.08 (0.31–3.71)	1.000	0.76 (0.22–2.6)	0.663
COPD	12 (46)	1.00 (ref.)		1.00 (ref.)	

*Adjusted for age, gender, and prevaccination titer.

short period from the time when the influenza vaccine became available to vaccination before the anticipated winter outbreak of influenza infection. Inclusion of more cases may provide more definitive results, particularly when considering the effects of different chemotherapy regimens on patients with lung cancer. Second, in our study, there was the possibility of intercurrent asymptomatic infections. However, we monitored all patients for influenza-like illness, and no patients experienced confirmed influenza virus infections during the study period. Thus, we believe that the effect of intercurrent infection was not large enough to invalidate the present results. Third, healthy controls were not evaluated in this study. However, we evaluated patients with COPD as a immunocompetent control group; these patients were considered appropriate based on their high sPs. Fourth, the antibody titers at the end of season were not evaluated in the present study because we wanted to focus on the antibody titers before vaccination and at 4–6 weeks after vaccination. We thought that the immunogenicity at 4–6 weeks after vaccination was clinically important for evaluating the immunoprotective ability against influenza infection during the influenza season.

In conclusion, patients with lung cancer undergoing chemotherapy showed an acceptable immune response to the trivalent influenza vaccine without significant adverse effects, supporting the recommendation for annual influenza vaccination in patients with lung cancer. Further studies assessing influenza vaccine efficacy in patients with cancer are needed to strengthen the evidence supporting influenza vaccination in these patients.

Materials and methods

Study design and patients

In November and December 2013, patients with lung cancer undergoing chemotherapy and patients with COPD being treated at the Department of Pulmonary Medicine, Kameda Medical Center, Chiba, Japan were invited to participate in this study. We chose patients with COPD as immunocompetent controls because these patients are a priority group for influenza vaccination,[32,33] and most patients with COPD receive the influenza vaccine annually in Japan.

The inclusion criteria were as follows: 1) patients with lung cancer who underwent anticancer chemotherapy with cytotoxic agents from 2 weeks before influenza vaccination to 4 weeks after vaccination, or 2) patients with COPD diagnosed based on a postbronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1 /FVC) of less than 70%.[36] Exclusion criteria were as follows: a history of influenza infection, an acute febrile illness or evidences of severe acute illness at the time of vaccination, a history of allergy due to vaccine components, or other contraindications for receiving the vaccine.

All patients provided written informed consent after the nature and possible consequences of the study were explained. The study protocol was approved by the Research Ethics Committee of the Kameda Medical Center (No. 13–061) and was performed in accordance with the Declaration of Helsinki. After obtaining informed consent, the baseline patient characteristics, including age, gender, histological type of lung cancer, clinical stage of lung cancer, stage of COPD according to the

Table 5. Odds ratios for seroprotection rates at after trivalent influenza vaccination in patients with lung cancer or COPD.

	Seroprotection rate (sP) (≥1:40): n (%)	Crude analysis		Multivariate analysis*	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
A/California/7/2009(H1N1)pdm09					
Lung cancer	21 (84)	1.24 (0.23–7.21)	1.000	1.56 (0.28–8.84)	0.613
COPD	21 (81)	1.00 (ref.)		1.00 (ref.)	
A/Texas/50/2012(H3N2)					
Lung cancer	21 (84)	0.22 (0.00–2.40)	0.191	0.30 (0.02–4.01)	0.364
COPD	25 (96)	1.00 (ref.)		1.00 (ref.)	
B/Massachusetts/02/2012					
Lung cancer	16 (64)	0.15 (0.01–0.88)	0.019	0.11 (0.01–0.79)	0.028
COPD	24 (92)	1.00 (ref.)		1.00 (ref.)	

*Adjusted for age, gender, and prevaccination titer.

Table 6. Immune response to the trivalent influenza vaccine in patients with lung cancer, according to the type of chemotherapy.

	Geometric mean titer[a]		Mean fold rise[a] S1/S0	After vaccination[b]		
	Before vaccination (S0)	After vaccination (S1)		Seroprotection rate (sP) (≥1:40): n (%)	Seroresponse rate (sR) (≥4 fold-rise): n (%)	Seroconversion rate (sC) : n (%)
A/California/7/2009(H1N1) pdm09						
Single agent	12	160	13.0	10 (100)	8 (80)	8 (80)
Platinum doublet	10	80	7.6	11 (73)	10 (67)	10 (67)
	($P = 0.809$)	($P = 0.306$)	($P = 0.415$)	($P = 0.125$)	($P = 0.659$)	($P = 0.659$)
A/Texas/50/2012(H3N2)						
Single agent	16	184	11.3	10 (100)	8 (80)	8 (80)
Platinum doublet	22	80	3.6	11 (73)	8 (53)	6 (40)
	($P = 0.590$)	($P = 0.143$)	($P = 0.049$)	($P = 0.125$)	($P = 0.229$)	($P = 0.099$)
B/Massachusetts/02/2012						
Single agent	12	80	6.5	7 (70)	8 (80)	5 (50)
Platinum doublet	13	42	3.2	9 (60)	7 (47)	7 (47)
	($P = 0.254$)	($P = 0.324$)	($P = 0.122$)	($P = 0.691$)	($P = 0.211$)	($P = 1.000$)

[a]Wilcoxon rank-sum tests were performed for intercategory comparisons.
[b]Seroprotection rates, seroresponse rates, and seroconversion rates were compared between groups by Fisher's exact test.

Global Initiative for Chronic Obstructive Lung Disease criteria,[33,36] smoking status, and type of chemotherapy, were collected.

Vaccination

FLUBIK HA Syringe (Research Foundation for Microbial Diseases of Osaka University, Osaka, Japan) containing inactivated A/California/7/2009 (H1N1) pdm09, A/Texas/50/2012 (H3N2), and B/ Massachusetts/2/2012 (B/Yamagata lineage) was administered as a single subcutaneous injection, the typical administration route used in Japan. Each vaccine contained 15 μg hemagglutinin antigen of each strain. The vaccine did not contain thimerosal. The vaccine was prepared in embryonated chicken eggs using standard methods for the production of trivalent inactivated vaccine. Attending physicians monitored all patients until April 2014 and evaluated the occurrence of side effects from the vaccine or of influenza infection.

Measurement of antibody titers

Serum samples were collected before vaccination (S0) and at 4–6 weeks after vaccination (S1). All serum specimens were kept at −40°C until analysis. Serum antibody levels to hemagglutinin were measured according to the standard microtiter hemagglutination inhibition method[37] with the same antigens as used in the vaccine. During the measurement process, none of the 3 antigens was treated with ether. All samples were assayed at the Research Foundation for Microbial Diseases of Osaka University, Osaka, Japan in June 2014.

Statistical analyses

The following outcomes were calculated to evaluate the immunogenicity of influenza vaccine: GMT, MFR, sP (postvaccination titer > 1:40), and sR (> 4-fold rise), sC (a prevaccination titer < 1:10 and a postvaccination titer ≥ 1:40 or a prevaccination titer ≥ 1:10 and a minimum 4-fold rise in postvaccination titer). During data processing, titers of less than 1:10 were regarded as 1:5, and reciprocal antibody titers were analyzed after logarithmic transformation. The results are presented in the original scale by calculating the antilogarithm. Stratified analyses were performed to examine the effects of the following potential confounders: age at vaccination (<69 and ≥69 years), gender (men versus women), prevaccination titer (<1:10 and ≥1:10), and underlying diseases (lung cancer and COPD). The significance of fold rise within a category was assessed by the Wilcoxon signed-rank test, and intercategory comparisons were made by the Wilcoxon rank-sum test. Student's t tests or Fisher's exact tests were performed where appropriate. In addition, the independent effects of potential confounders on antibody induction were assessed by logistic regression. The models were constructed with sP, sR, and sC as the dependent variables and with the above-mentioned potential confounders as the explanatory variables. ORs and 95% confidence intervals (CIs) were calculated. All tests were 2-sided, and all analyses were performed using R version 3.2.3 (R foundation for Statistical Computing; http://www.r-project.org). Differences with p values less than 0.05 were considered significant.

Abbreviations

COPD	chronic obstructive pulmonary disease
sP	seroprotection rate
GMT	geometric mean titer
MFR	mean fold rise
sR	seroresponse rate
OR	odds ratio
95% CI	95% confidence interval

Disclosure of potential conflicts of interest

The authors declare that they have no conflicts of interest.

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References

[1] Cooksley CD, Avritscher EB, Bekele BN, Rolston KV, Geraci JM, Elting LS. Epidemiology and outcomes of serious influenza-related infections in the cancer population. Cancer 2005; 104:618-28; PMID:15973737; http://dx.doi.org/10.1002/cncr.21203

[2] Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. Lancet Infect Dis 2009; 9:493-504; PMID:19628174; http://dx.doi.org/10.1016/S1473-3099(09)70175-6

[3] Shehata MA, Karim NA. Influenza vaccination in cancer patients undergoing systemic therapy. Clin Med Insights Oncol 2014; 8:57-64; PMID:24855405

[4] Earle CC. Influenza vaccination in elderly patients with advanced colorectal cancer. J Clin Oncol 2003; 21:1161-6; PMID:12637485; http://dx.doi.org/10.1200/JCO.2003.06.008

[5] Beck CR, McKenzie BC, Hashim AB, Harris RC, Zanuzdana A, Agboado G, Orton E, Bechard-Evans L, Morgan G, Stevenson C, et al. Influenza vaccination for immunocompromised patients: systematic review and meta-analysis from a public health policy perspective. PLoS One 2011; 6:e29249; PMID:22216224; http://dx.doi.org/10.1371/journal.pone.0029249

[6] Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014; 58:309-18; PMID:24421306; http://dx.doi.org/10.1093/cid/cit816

[7] Loulergue P, Mir O, Alexandre J, Ropert S, Goldwasser F, Launay O. Low influenza vaccination rate among patients receiving chemotherapy for cancer. Ann Oncol 2008; 19:1658; PMID:18662953; http://dx.doi.org/10.1093/annonc/mdn531

[8] Meidani M, Rostami M, Dehghani F. Why coverage of influenza vaccine is not enough in patients receiving chemotherapy? Int J Prev Med 2011; 2:186-7; PMID:21811662

[9] Anderson H, Petrie K, Berrisford C, Charlett A, Thatcher N, Zambon M. Seroconversion after influenza vaccination in patients with lung cancer. Br J Cancer 1999; 80:219-20; PMID:10389999; http://dx.doi.org/10.1038/sj.bjc.6690342

[10] Kim DH, Lee YY, Shin US, Moon SM. Immunogenicity of influenza vaccine in colorectal cancer patients. Cancer Res Treat 2013; 45:303-12; PMID:24454003; http://dx.doi.org/10.4143/crt.2013.45.4.303

[11] Xu Y, Methuku N, Coimbatore P, Fitzgerald T, Huang Y, Xiao YY, Pagala M, Gupta S, Solomon W, Rubin P, et al. Immunogenicity of an inactivated monovalent 2009 influenza A (H1N1) vaccine in patients who have cancer. Oncologist 2012; 17:125-34; PMID:22240540; http://dx.doi.org/10.1634/theoncologist.2011-0220

[12] Global Burden of Disease Cancer Collaboration. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, Allen C, Hansen G, Woodbrook R, et al. The Global Burden of Cancer 2013. JAMA Oncol 2015; 1:505-27; PMID:26181261; http://dx.doi.org/10.1001/jamaoncol.2015.0735

[13] Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S, Jr, Brahmer JR, Ellis PM, Gajra A, Rackear N, Schiller JH, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015; 33:3488-515; PMID:26324367; http://dx.doi.org/10.1200/JCO.2015.62.1342

[14] European Committee for Proprietary Medial Products. Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP/BWP/214/96). London: European Agency Evaluation Medical Products, 1997.

[15] Center for Biologics Evaluation and Research. Guidance for industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines. Food Drug Administration, 2007.

[16] Beck CR, McKenzie BC, Hashim AB, Harris RC, University of Nottingham I, the ImmunoCompromised Study G, Nguyen-Van-Tam JS. Influenza vaccination for immunocompromised patients: systematic review and meta-analysis by etiology. J Infect Dis 2012; 206:1250-9; PMID:22904335; http://dx.doi.org/10.1093/infdis/jis487

[17] Robertson JD, Nagesh K, Jowitt SN, Dougal M, Anderson H, Mutton K, Zambon M, Scarffe JH. Immunogenicity of vaccination against influenza, Streptococcus pneumoniae and Haemophilus influenzae type B in patients with multiple myeloma. Br J Cancer 2000; 82:1261-5; PMID:10755398; http://dx.doi.org/10.1054/bjoc.1999.1088

[18] Ljungman P, Nahi H, Linde A. Vaccination of patients with haematological malignancies with one or two doses of influenza vaccine: a randomised study. Br J Haematol 2005; 130:96-8; PMID:15982350; http://dx.doi.org/10.1111/j.1365-2141.2005.05582.x

[19] Mazza JJ, Yale SH, Arrowood JR, Reynolds CE, Glurich I, Chyou PH, Linneman JG, Reed KD. Efficacy of the influenza vaccine in patients with malignant lymphoma. Clin Med Res 2005; 3:214-20; PMID:16303886; http://dx.doi.org/10.3121/cmr.3.4.214

[20] Yri OE, Torfoss D, Hungnes O, Tierens A, Waalen K, Nordoy T, Dudman S, Kilander A, Wader KF, Ostenstad B, et al. Rituximab blocks protective serologic response to influenza A (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment. Blood 2011; 118:6769-71; PMID:22058114; http://dx.doi.org/10.1182/blood-2011-08-372649

[21] Hodges GR, Davis JW, Lewis HD, Jr, Whittier FC, Jr, Siegel CD, Chin TD, Clark GM, Noble GR. Response to influenza A vaccine among high-risk patients. South Med J 1979; 72:29-32; PMID:366766; http://dx.doi.org/10.1097/00007611-197901000-00010

[22] Brydak LB, Machala M, Centkowski P, Warzocha K, Bilinski P. Humoral response to hemagglutinin components of influenza vaccine in patients with non-Hodgkin malignant lymphoma. Vaccine 2006; 24:6620-3; PMID:16870313; http://dx.doi.org/10.1016/j.vaccine.2006.05.100

[23] Puthillath A, Trump DL, Andrews C, Bir A, Romano K, Wisniewski M, Fakih MG. Serological immune responses to influenza vaccine in patients with colorectal cancer. Cancer Chemother Pharmacol 2011; 67:111-5; PMID:20204362; http://dx.doi.org/10.1007/s00280-010-1292-2

[24] Brydak LB, Guzy J, Starzyk J, Machala M, Gozdz SS. Humoral immune response after vaccination against influenza in patients with breast cancer. Support Care Cancer 2001; 9:65-8; PMID:11147146; http://dx.doi.org/10.1007/s005200000186

[25] Vilar-Compte D, Cornejo P, Valle-Salinas A, Roldan-Marin R, Iguala M, Cervantes Y, Lopez I. Influenza vaccination in patients with breast cancer: a case-series analysis. Med Sci Monit 2006; 12:CR332-6; PMID:16865064

[26] Kendal AP, Cate TR. Increased sensitivity and reduced specificity of hemagglutination inhibition tests with ether-treated influenza B/Singapore/222/79. J Clin Microbiol 1983; 18:930-4; PMID:6630472

[27] Tsurudome Y, Kimachi K, Okada Y, Matsuura K, Ooyama Y, Ibaragi K, Kino Y, Ueda K. Immunogenicity and safety of an inactivated quadrivalent influenza vaccine in healthy adults: a phase II, open-label, uncontrolled trial in Japan. Microbiol Immunol 2015; 59:597-604. accessed at ; PMID:26272602; http://dx.doi.org/10.1111/1348-0421.12316

[28] Francis T, Salk JE, Quilligan JJ. Experience with vaccination against influenza in the spring of 1947: A preliminary report. Am J Public Health Nations Health 1947; 37:1013-6; http://dx.doi.org/10.2105/AJPH.37.8.1013

[29] Ndifon W. A simple mechanistic explanation for original antigenic sin and its alleviation by adjuvants. J R Soc Interface 2015; 12:20150627; PMID:26577593; http://dx.doi.org/10.1098/rsif.2015.0627

[30] Skowronski DM, Hottes TS, De Serres G, Ward BJ, Janjua NZ, Sabaiduc S, Chan T, Petric M. Influenza B/Victoria antigen induces strong recall of B/Yamagata but lower B/Victoria response in children primed with two doses of B/Yamagata. Pediatr Infect Dis J 2011; 30:833-9; PMID:21857263; http://dx.doi.org/10.1097/INF.0b013e31822db4dc

[31] Ministry of Health, Labour and Welfare, Japan. Stratgey for prevention of influenza infection. Available at: http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou01/dl/fludoco1415.pdf (accessed June 25, 2016)
[32] Fiore AE, Shay DK, Broder K, Iskander JK, Uyeki TM, Mootrey G, Bresee JS, Cox NJ, Centers for Disease C, Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recommendations Reports 2009; 58:1-52.
[33] Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015. Available from: http://www.goldcopd.org/
[34] Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006; CD002733; PMID:16437444
[35] Nath KD, Burel JG, Shankar V, Pritchard AL, Towers M, Looke D, Davies JM, Upham JW. Clinical factors associated with the humoral immune response to influenza vaccination in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2014; 9:51-6; PMID:24399872
[36] Qaseem A, Snow V, Shekelle P, Sherif K, Wilt TJ, Weinberger S, Owens DK, Clinical Efficacy Assessment Subcommittee of the American College of P. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. Annals Internal Med 2007; 147:633-8; PMID:17975186; http://dx.doi.org/10.7326/0003-4819-147-9-200711060-00008
[37] Hirst GK. The quantitative determination of influenza virus and antibodies by means of red cell agglutination. J Exp Med 1942; 75:49-64; PMID:19871167; http://dx.doi.org/10.1084/jem.75.1.49