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BRIEF REPORT

Immunogenicity of Influenza Vaccination in Patients with Cancer Receiving Immune Checkpoint Inhibitors

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Among prospectively enrolled adult patients with cancer receiving immune checkpoint inhibitors (ICIs; n = 46) or cytotoxic agents (n = 90), seroprotection and seroconversion rates after seasonal quadrivalent influenza vaccinations were higher with ICI than with cytotoxic chemotherapy. These results support annual influenza vaccinations for cancer patients receiving ICIs.

Clinical Trials Registration. clinicaltrials.gov (NCT03590808).

Keywords. influenza; vaccination; immune checkpoint inhibitor; immunogenicity; immune-related adverse event.

Patients who receive chemotherapy for cancer are at increased risk of infection with influenza virus, which causes significant morbidity [1]. Annual vaccinations are recommended for patients with cancer who receive chemotherapy, because they reduce influenza virus infections and complications [2].

Immune checkpoint inhibitors (ICIs) recently became the standard treatment for various types of cancer [3]. However, among patients with cancer who receive ICIs, influenza vaccination efficacy has not been sufficiently evaluated. As physicians' concerns regarding vaccine efficacy and safety contribute to the lack of influenza vaccination among patients with cancer, these issues require urgent elucidation.

The present study aimed to compare the immunogenicity of quadrivalent influenza vaccine between patients with cancer who received ICIs and those who received cytotoxic chemotherapy.

METHODS

Study Design and Vaccination

From September to November 2018, we prospectively enrolled patients with cancer who received either ICIs or cytotoxic chemotherapy at 2 tertiary hospitals. Additional inclusion criteria were as follows: age older than 20 years, Eastern Cooperative Oncology Group performance status of 0 or 1, and normal hematological, renal, and hepatic function. We excluded patients who had allergies to eggs or vaccine components, had previous seasonal influenza vaccinations, received only molecular-targeting agents, had active infections, received immunosuppressive agents, or had human immunodeficiency virus infections.

Written informed consent was obtained from all participants prior to vaccination. The study was approved by the Institutional Review Boards of both hospitals (IRB No. H-1806-088-951 and B-1808/484-402). The study was registered at ClinicalTrials.gov (NCT03590808).

All participants received an intramuscular seasonal quadrivalent influenza vaccine (GCFLU Quadrivalent Pre-filled Syringe injection. [2018/2019]; GC Pharma). Each 0.5-mL dose contained 15 μg of purified viral antigen from the strains: A/Singapore/GP1908/2015 IVR-180 (H1N1), A/Singapore/INFIMH-16–0019/2016 IVR-186 (H3N2), B/Phuket/3073/2013 (Yamagata), and B/Maryland/15/2016 NYMC BX-69A (Victoria). The vaccine was administered concomitantly on day 1 of the chemotherapeutic cycle. Concurrent administration of the vaccine with cytotoxic chemotherapy was previously found to be as immunogenic as vaccination at other time points in the chemotherapy cycle [4].

Immunogenicity

Follow-up serum samples were obtained after 4 (±1) weeks (day 21 to 35) to examine serum hemagglutination inhibition (HAI) antibody titers. All samples were stored at −70°C until assayed. The primary outcome was the seroprotection rate, defined as the percentage of patients with serum HAI antibody titers of 1:40 or greater. The prespecified secondary outcomes were (1) the seroconversion rate, defined as the proportion of patients who showed an increase in antibody titers from less than 1:10 to 1:40 or greater or a 4-fold or more increase from a prevaccination titer of more than 1:10, and (2) the geometric

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mean titers (GMTs) before and after vaccination. Subgroup analyses for seroprotection rates were performed according to age (≤60 vs >60 years), previous influenza vaccination history, baseline HAI antibody titers, and cancer type. We performed a post hoc multivariable analysis to identify factors associated with seroprotection based on the number of strains targeted by serum antibodies.

The HAI antibody assays were performed in duplicate at Vaccine Bio Institute (Seoul, South Korea), as described previously [5]. Titers below the detection limit (<1:10) were designated 1:5.

Safety

Adverse events were evaluated at 2 to 4 days postvaccination with a telephone call and at 21 to 35 days postvaccination with a questionnaire at the clinic. Standard scales were used to grade adverse events and to classify vaccination causality [6–8]. Vaccine-related adverse events were defined as events that were possibly or likely associated with the immunization.

Immune-related adverse events (irAEs) were monitored until 6 months after the vaccination with predefined measures, including a clinical examination every visit; a chest radiography, complete blood count, and serum chemistry test at least every month; a thyroid function test every 8 weeks; and additional tests, when required.

Statistical Analysis

The null hypothesis of the present study was that the seroprotection rate for each strain would not be different between the ICI and cytotoxic chemotherapy groups.

For a power analysis, the estimated seroprotection rate was 65% in the cytotoxic chemotherapy group [4] and it was assumed to be 85% in the ICI group, which is higher than the rate in the cytotoxic chemotherapy group and comparable to that of healthy adults [9]. We calculated the sample size with a 1-sided test, a .05 α error, and a .2 β error. We assumed a 1:2 ratio for ICI:cytotoxic seroprotection rates. Thus, ICI and cytotoxic chemotherapy groups required 43 and 86 patients, respectively. Considering a presumed 10% drop-out rate, the ICI and cytotoxic chemotherapy groups required 48 and 95 patients, respectively.

We compared continuous and categorical variables between the groups with the *t* test and chi-square test or Fisher's exact test, respectively. Multivariable linear regression analyses were performed to investigate independent associations between clinical variables and the cumulative numbers of strains detected in seroprotection tests. The model included age older than 60 years and variables that achieved $P < .05$ in the univariable analysis.

We calculated 1-sided *P* values for analyzing seroprotection or seroconversion rates and GMTs of HAI antibodies. Otherwise, 2-sided *P* values <.05 were considered significant. The Benjamini-Hochberg method was used to calculate *P* values for the seroprotection rates of 4 strains to adjust the multiple-comparison analysis of the primary outcome. All statistical analyses were performed with SPSS for Windows (version 22; IBM Corporation).

RESULTS

Patients

During the study period, we assessed 49 and 105 patients for eligibility in the ICI and cytotoxic chemotherapy groups, respectively (Supplementary Figure 1). Among 48 and 95 patients who were vaccinated, 46 and 90 patients were finally examined for postvaccination HAI antibody titers, which satisfied the group size requirements.

The most common cancer was lung cancer in both groups (Supplementary Table 1). Nivolumab and pembrolizumab were the most commonly used ICIs in this study. The proportion of patients vaccinated in the last influenza season or within the past 3 years and the proportion of baseline HAI antibody titers of 1:40 or greater for each strain were not significantly different between groups.

No patient had laboratory-confirmed symptomatic influenza during the 2018/2019 season.

Immunogenicity

The seroprotection and seroconversion rates were significantly higher in the ICI group than in the cytotoxic chemotherapy group for all strains, except for the H1N1 strain (Table 1). Postvaccination GMTs for HAI antibodies were significantly higher in the ICI group for all strains, after adjusting for prevaccination GMTs (Supplementary Table 2).

The proportions of cumulative strains detected in seroprotection or seroconversion tests were significantly higher in the ICI than in the cytotoxic chemotherapy group (Figure 1). We found an independent association between ICI and the number of strains protected against, after adjusting for age older than 60 years, cancer type, and baseline HAI antibody titers (Supplementary Table 3). In all subgroup analyses, the ICI group showed a tendency toward higher seroprotection rates than the cytotoxic chemotherapy group (Supplementary Table 4).

Safety

Among 47 and 92 patients in the ICI and cytotoxic chemotherapy groups, respectively, the rates of conventional adverse events were comparable (Supplementary Table 5). Among patients receiving ICI, we identified 4 (9%) irAEs during the follow-up period, all of which were grade 1 (Supplementary Table 6).

DISCUSSION

This study compared the immunogenicity of influenza vaccination between patients with cancer who received either ICIs

Table 1. Seroprotection and Seroconversion Rates in the Immune Checkpoint Inhibitor and Cytotoxic Chemotherapy Groups After Receiving a 2018/2019 Season Influenza Vaccination

Variable and Influenza Strain	Percentage of Patients (95% CI)		Difference (95% CI)	*P*[a]
	ICI (n = 46)	Cytotoxic (n = 90)		
Seroprotection				
H1N1	76 (63 to 89)	68 (58 to 78)	8 (−8 to 24)	.111
H3N2	89 (80 to 98)	70 (60 to 80)	19 (6 to 32)	.005
B-Yamagata	83 (71 to 94)	54 (44 to 65)	28 (13 to 44)	.002
B-Victoria	85 (74 to 96)	48 (37 to 58)	37 (22 to 52)	<.001
Seroconversion				
H1N1	57 (42 to 71)	39 (29 to 49)	18 (0 to 35)	.086
H3N2	52 (37 to 67)	27 (17 to 36)	26 (8 to 43)	.006
B-Yamagata	54 (39 to 69)	30 (20 to 40)	24 (7 to 42)	.007
B-Victoria	65 (51 to 80)	28 (18 to 37)	37 (21 to 54)	<.001

Abbreviations: CI, confidence interval; ICI, immune checkpoint inhibitor.

[a]Adjusted to prevaccination hemagglutination inhibition antibody titers. *P* values for seroprotection rates were calculated with the Benjamini-Hochberg method of adjusting for multiple comparisons with 4 strains.

or cytotoxic chemotherapy. The quadrivalent influenza vaccine was more immunogenic in the ICI group than in the cytotoxic chemotherapy group. Further, only 9% of patients receiving ICI therapy developed an irAE and the 4 irAEs that occurred were mild in severity. These results suggest that annual influenza vaccination should be recommended in patients with cancer treated with ICIs.

It has been shown that influenza vaccinations yielded a lower humoral response in patients with solid cancer undergoing cytotoxic chemotherapy than in healthy controls [2]. Nevertheless, these vaccinations have been widely recommended for patients with cancer who receive cytotoxic chemotherapy, because its benefits far outweigh the risks. According to the European Agency for the Evaluation of Medical Products, the immunogenicity criteria for an adequate response to an influenza vaccination in healthy volunteers include seroprotection rates greater than 70% for each strain in patients aged 18 to 60 years and greater than 60% for patients older than 60 years [10]. Considering these criteria, our data suggested that the immunogenicity of the influenza vaccination was comparable between patients with cancer who received ICIs and healthy adults. These findings might reduce clinicians' hesitations in vaccinating patients under ICI treatment.

The safety of influenza vaccinations has been controversial for patients with cancer who receive ICIs [11, 12]. Although our cohort size was limited, we prospectively found a 9% incidence of irAEs, based on predefined measures. This finding implied that the potential risk of irAEs triggered by influenza vaccination was not substantial.

This study had some limitations. First, we evaluated humoral responses, rather than the incidence of clinical influenza infections, which might have required a larger sample size. Second, the number of patients in the ICI group was limited. Third, we did not compare the rate of irAEs between vaccinated and unvaccinated patients receiving ICIs, which precluded a definitive conclusion on the irAE rate.

In conclusion, influenza vaccination achieved higher levels of immunity in patients with cancer treated with ICIs compared

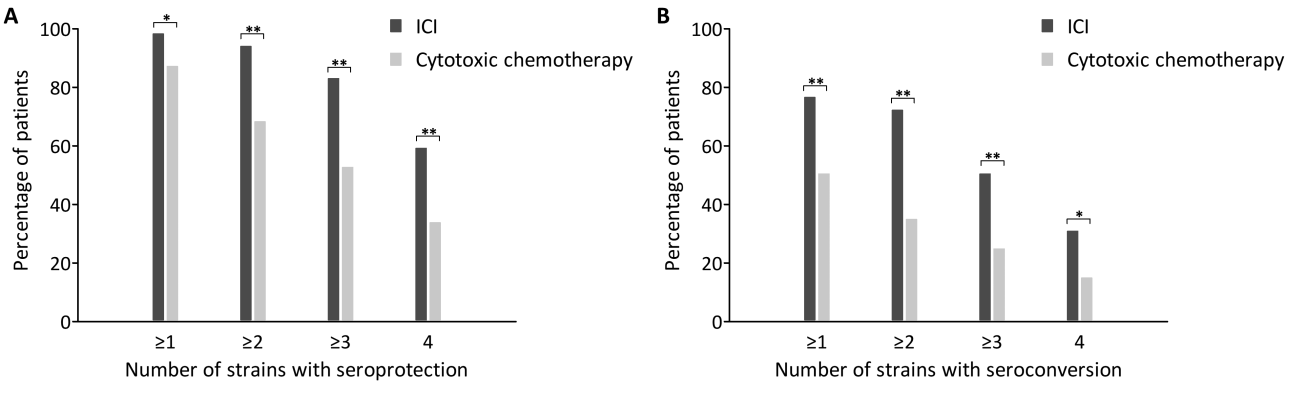

Figure 1. Numbers of seroprotective (*A*) and seroconverted (*B*) strains in the ICI and cytotoxic chemotherapy groups. **P* < .05, ***P* < .01. Abbreviation: ICI, immune checkpoint inhibitor.

with those receiving cytotoxic chemotherapy. In an effort to reduce the risk of influenza-associated morbidity and mortality in patients receiving ICIs, annual vaccination should be encouraged.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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