Safety of Inactivated Influenza Vaccine in Cancer Patients Receiving Immune Checkpoint Inhibitors

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Background. Cancer patients are at a higher risk for developing influenza (flu)-related complications. It is unclear if the flu vaccine exacerbates immune events in patients treated with immune checkpoint inhibitors (ICIs).

Methods. We conducted an institutional review board-IRB-approved retrospective review of advanced cancer patients on ICIs who received the flu vaccine during three consecutive seasons: 2014–2015, 2015–2016, and 2016–2017. The primary outcome assessed was any “new onset” immune-related adverse event (IRAE). A subset analysis of vaccinated patients newly treated with anti-programmed cell death protein 1 (PD-1) agents (nivolumab or pembrolizumab) was conducted to assess overall IRAE rates for comparison with published clinical trials.

Results. During the three seasons, 370 patients met criteria for ICI and vaccination within ~two approximately 2 months (65 days). The most common underlying cancers were lung (46%) and melanoma (19%); 61% of patients received an anti-PD-1 agent only. In the entire cohort, 20% experienced an IRAE (any grade); incidence of grade 3 or 4 toxicity was 8%. No grade 5 events occurred. In the subset of 170 patients newly treated with anti-PD-1 agents, the overall IRAE rate was 18% and, grade 3/4 events occurred in 7.6%. Influenza was diagnosed in 2 patients.

Conclusions. No increase in incidence or severity of IRAEs was detected in patients on ICIs who received the inactivated influenza vaccine within ~approximately 2 months of ICI. For newly treated patients on anti-PD-1 agents, IRAE rates were comparable to those from published clinical trials and did not vary with order of administration. Routine seasonal flu vaccination is encouraged in patients on ICIs.

Keywords. immune checkpoint inhibitors; influenza vaccine; safety.

Immune checkpoint inhibitors (ICIs) are the new frontier in cancer treatment. Cancer cells can evade the antitumor effect of the immune system. Checkpoint blockade overcomes this by targeting certain proteins that block the inhibitors of T-cell activation; these include programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte associated protein 4 (CTLA4). These drugs hold immense promise and are US Department of Agriculture (FDA) approved for a growing list of cancer types such as melanoma, non-small cell lung cancer, renal and bladder cancer, head and neck cancers, and certain lymphomas [1–3]. The enhanced T-cell activity is commonly associated with immune-mediated events that target host tissues [4].

Patients with underlying cancer are at a higher risk for developing influenza (flu)-related complications [5–7]. Vaccination is

the primary protective strategy against influenza [8–10]. Although response to flu vaccine is diminished in patients who receive cytotoxic chemotherapy, individuals treated with ICIs produce robust humoral and T-cell responses that match those of healthy individuals and correlate with clinical protection from influenza [11].

Certain organ-specific autoimmune diseases are known to be rare complications of influenza infection but have seldom been attributed to influenza vaccination [12]. The most well characterized among these at a population level is postvaccine Guillain-Barré syndrome (GBS). The risk of GBS after seasonal influenza vaccine is extremely small, estimated to be between 1 and 2 additional cases per million doses [13]. The notion that flu vaccine can trigger unintended immune consequences in patients on ICIs is derived from animal studies that demonstrated enhanced T-cell response to viral antigens with PD-1 blockade [14]. Further, it is postulated that vaccine may stimulate an overwhelming expansion of autoreactive T-cell clones that cross-recognize vaccine and self-antigens.

A recent small study from Switzerland described an unexpectedly high incidence of immune-related adverse events (IRAEs; 52%) among vaccinated patients on PD-1 inhibitors [15]. This report raises concerns around the safety of flu vaccine. Despite the Advisory Committee on Immunization Practices

Received 3 January 2019; editorial decision 27 February 2019; accepted 6 March 2019; published online March 15, 2019.

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Clinical Infectious Diseases® 2020;70(2):193–9

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(ACIP) recommendation for annual flu vaccination [13], many clinicians defer seasonal vaccination of patients on ICIs.

If flu vaccine poses an exaggerated risk of IRAEs in patients on ICIs, larger studies are needed to clarify a possible association. Our aim in this study was to determine incidence and severity of new onset IRAEs in patients who receive influenza vaccine within 2 months of any ICI therapy across 3 consecutive influenza seasons.

METHODS

This study was conducted at a tertiary care cancer center in New York City. We conducted a retrospective review of patients with advanced cancer who received an inactivated influenza vaccine within 2 months (65 days) of ICI administration. Recent or persistent viral antigenic exposure can induce changes in PD-1 signaling. This is postulated as a trigger of autoimmunity with ICIs. The possibility of vaccine administration before but near ICI administration was also explored as a possible association in this study. This cohort therefore included ICI naive and experienced individuals, that is, patients vaccinated before or after any dose of ICI, including patients who had been on ICI therapy >65 days prior to vaccination. Electronic pharmacy records were used to identify all patients with cancer who received an influenza vaccine at the study institution with at least 1 of the following FDA-approved agents administered within 65 days: ipilimumab (CTLA4 inhibitor), or pembrolizumab or nivolumab (anti-PD-1 agents). These immunotherapy agents were dosed per their FDA-approved schedule, as clinically indicated, for example, every 2 or 4 weeks for nivolumab or every 3 weeks for pembrolizumab. Dosing of immunotherapy was continued until progression or unmanageable side-effects.

Influenza vaccine is offered between September and April each season. The type of vaccine (high dose vs standard dose; quadrivalent vs trivalent) was also collected. Adjuvanted vaccines against influenza were not used during the study period. Electronic medical records were reviewed for clinicopathologic parameters related to any grade “new onset” IRAE as defined by the Common Terminology Criteria for Adverse Events, version 4.0. This grading system refers to the severity of the adverse event associated with cancer therapy as follows: grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life threatening; and grade 5, death (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm). Only newly occurring IRAEs after vaccine and ICI were included. Data on age at time of vaccination, sex, tumor type, dates of ICI administration, and type(s) of ICI were also collected. Data on IRAE incidence and death were collected through 27 March 2018. To determine whether rates of IRAEs appeared to be increased among ICI recipients who received influenza vaccine, results from the present study were compared to those from historical studies that did not select participants on the basis of influenza vaccination.

The study was conducted over 3 consecutive influenza seasons: 2014–2015, 2015–2016, and 2016–2017. Influenza season is defined by criteria set by the Influenza Surveillance Division of the New York State Department of Health (<https://health.ny.gov>). Influenza-like illness (ILI) is defined as an acute respiratory illness with fever $\geq 38^{\circ}\text{C}$ and cough, with onset of symptoms within the past 10 days. Screening for ILI is routinely performed at the study institution, and diagnostic testing for influenza is undertaken if criteria are met or at the clinician's discretion. Testing for influenza (A and B) is performed as part of a multiple target BioFire Film Array Respiratory Panel (Bio Fire Diagnostics; Biomerieux). Laboratory-confirmed cases of influenza and data related to ILI were extracted from institutional databases. The Institutional Review Board of Memorial Sloan Kettering Cancer Center reviewed and approved the study.

Statistical Analyses

We conducted bivariate analyses (2-sample *t* tests and χ^2 tests for independence) to determine whether incidence of any grade new onset IRAE differed according to age, sex, tumor type (lung, melanoma, other), therapy type (ipilimumab only, ipilimumab followed by anti-PD-1, ipilimumab [3 mg/kg] concurrently with nivolumab [1 mg/kg], anti-PD-1 only, or other [1 of these drugs in combination with an experimental agent or an agent in another class]), influenza season, vaccine dose (high vs standard), and vaccine coverage (trivalent vs quadrivalent). Since high-dose vaccine is indicated for older patients and because all high-dose vaccines administered were trivalent, we used multivariable logistic regression to assess confounding between age and vaccine dose and between vaccine dose and vaccine coverage.

To account for the fact that most IRAEs occur during the first 2 months of treatment and specifically investigate the risk with anti-PD-1 agents, we performed a subanalysis to characterize IRAE rates in patients who were vaccinated within 65 days before or after receiving the first dose of anti-PD-1 agent. Individuals with lung cancer on nivolumab accounted for most patients in this subanalysis. To examine the effects of treatment order (vaccine first, ICI first, or vaccination on the same day as beginning treatment with ICI) in this subgroup, we used stratified Kaplan-Meier product-limit survival estimates to model survival (ie, not having an IRAE). Patients began contributing person-time to this model after having received at least 1 dose of anti-PD-1 agent and influenza vaccine. Patients were considered to be on ICI therapy once they received the first dose; the timing of subsequent doses was not a factor in this analysis.

RESULTS

During the 3 seasons, 370 patients received flu vaccine within 65 days of treatment with ICI. Collectively these patients received 5873 doses at the study institution (median, 8; range,

1–133). The median duration of treatment was 139 days (4.5 months), and median duration of follow-up until death or end of data collection was 512 days (1.4 years).

Clinical characteristics of the cohort are presented in [Table 1](#). The main tumor types were lung (46%) and melanoma (19%). [Figure 1](#) shows a breakdown of various ICI therapies. Most patients (n = 227, 61%) received treatment with anti-PD-1 agents only (pembrolizumab and/or nivolumab), while 22% received combination treatment with ipilimumab plus nivolumab. For the 227 patients on anti-PD-1 agents, 170 received their first treatment dose during the study period.

Among the 370 patients, 75 (20%) experienced a new onset IRAE (any grade). Of the 75 IRAEs, 5 (7%) were grade 1, 40 (53%) were grade 2, 27 (36%) were grade 3, and 3 (4%) were grade 4; no grade 5 IRAEs were observed. The main types of IRAEs were endocrine (28% of all IRAEs) followed by pneumonitis (25%) and colitis or transaminitis (13% and 12%, respectively). IRAEs were managed with steroid or other immunosuppressive treatment (48%), treatment interruption (35%), or supportive medications (19%). In bivariate analyses,

no significant differences in risk of IRAEs were observed by sex, tumor type, therapy type, season, vaccine dose, or order of administration ([Table 1](#)). Patients who had an IRAE were significantly older and more likely to have received the trivalent vaccine. However, in multivariable analysis, high-dose vaccination was more common among older patients, and age was no longer significant after controlling for whether patients received high-dose vs standard-dose vaccine. Similarly, although IRAEs were significantly more common among patients who received trivalent vaccine, this is likely explained by the fact that all trivalent vaccines administered were high dose; after controlling for high vs standard dose in multivariable analysis, the effect of trivalent vs quadrivalent was no longer significant.

The proportion of patients who experienced any IRAE was significantly higher among those treated with ipilimumab plus nivolumab (25/82, 30%), although overall incidence in our cohort for this combination treatment is lower than published reports of 50%–55% ([Supplementary Table](#)). For patients on anti-PD-1, the overall IRAE rate was 17% (38/227); the proportion of patients who experienced serious (grade 3 or 4) IRAEs

Table 1. Differences Between Patients Who Developed an Immune-related Adverse Event and Those Who Did Not Among All Patients Who Received Immune Checkpoint Inhibitors and Influenza Vaccine

Variable	IRAE (n = 75)	No IRAE (n = 295)	PValue
Age at vaccination, y	65.9 (11.9)	62.2 (14.1)	.04
Sex			.52
Male (N = 200)	43 (21%)	157 (79%)	...
Female (N = 179)	32 (19%)	138 (81%)	...
Tumor type			.86
Lung (N = 165)	32 (19%)	133 (81%)	...
Melanoma (N = 71)	16 (23%)	55 (77%)	...
Other (N = 134)	27 (20%)	107 (80%)	...
Therapy type			.13
Ipilimumab only (N = 4)	1 (25%)	3 (75%)	...
Ipilimumab followed by anti-PD-1 (N = 15)	3 (20%)	12 (80%)	...
Ipilimumab and anti-PD-1 concurrently (N = 82)	25 (30%)	57 (70%)	...
Anti-PD-1 only (N = 227)	38 (17%)	189 (83%)	...
Other ^a (N = 42)	8 (19%)	34 (81%)	...
Season			.76
2014–2015 (N = 36)	9 (25%)	27 (75%)	...
2015–2016 (N = 137)	27 (20%)	110 (80%)	...
2016–2017 (N = 197)	39 (20%)	158 (80%)	...
Vaccine dose			.10
High (N = 171)	41 (24%)	130 (76%)	...
Standard (N = 199)	34 (17%)	165 (83%)	...
Vaccine coverage			.03
Quadrivalent (N = 163)	25 (15%)	138 (85%)	...
Trivalent (N = 207)	50 (24%)	157 (76%)	...
Order of administration			.20
Immunotherapy first (N = 232)	43 (19%)	189 (81%)	...
Vaccine first (N = 107)	22 (21%)	85 (79%)	...
Same day (N = 31)	10 (32%)	21 (68%)	...

For continuous variables, data are mean (standard deviation) with results of 1-sample t test. For categorical variables, data are number (%) of category with results of χ^2 test of independence. Abbreviations: anti-PD-1, anti-programmed cell death protein 1; IRAE, immune-related adverse event.

^aUS Food and Drug Administration–approved immune checkpoint inhibitors in combination with an experimental agent or an agent in another class.

ICI, immune checkpoint inhibitors; anti-PD1; anti-programmed death-1; NSCLC, non-small cell lung cancer

Figure 1. Flow diagram shows type of ICI for entire study cohort and population included in subset analysis (vaccinated patients who were newly treated with anti-PD-1 agents). Abbreviations: ICI, immune checkpoint inhibitors; anti-PD-1, anti-programmed cell death protein 1; NSCLC, non-small cell lung cancer.

was higher among those treated with nivolumab plus ipilimumab (11/82, 13%) than among those treated with anti-PD-1 agents alone (15/227, 6.6%).

Figure 2 provides a detailed illustration of the time from receipt of vaccine and ICI (immunotherapy) to IRAE for the 75 patients who experienced these events. Among the 82 patients treated with ipilimumab plus nivolumab, 42 received influenza vaccination within 65 days of beginning immunotherapy (first dose), and the incidence of grade 3 or grade 4 IRAEs was 24%.

Subanalysis of Patients Newly Treated With Anti-PD-1 Agents Only, Nivolumab or Pembrolizumab

For the 227 patients (Figure 1) treated with pembrolizumab or nivolumab, 170 were vaccinated within 65 days of beginning treatment with an anti-PD-1 agent. These 170 patients were included in the subset analysis. The median age was 67 years, and 52% were male. Most of the patients received nivolumab (77%). The median time between vaccine and anti-PD-1 was 24 days for vaccine first ($n = 76$) and 29 days for ICI first ($n = 73$ patients); 21 patients were vaccinated concomitantly with a first dose of anti-PD-1 on the start date. The median number of doses of anti-PD-1 agent was 5 (range, 1–59), 8 (range, 1–58), and 6 (range, 1–28) for patients who were vaccinated before, after, or on the same day as administration of the anti-PD-1 agent. The overall rate of IRAEs was 18% ($n = 31/170$); grade 3/4 events occurred in 7.6% of patients ($n = 13/170$). Figure 3 shows stratified Kaplan-Meier product-limit survival estimates to model survival (no IRAE) after having received both

anti-PD-1 agents and flu vaccine for the 3 groups comparing patients who were vaccinated before beginning anti-PD-1 treatment, patients who were vaccinated after beginning anti-PD-1 treatment, and patients who received the vaccine on the first day of anti-PD-1 treatment for patients receiving anti-PD-1 agents only. No significant difference in frequency of IRAEs was observed between the 3 groups ($P = .6$).

Specifically, for patients with non-small cell lung cancer within this subset, 103 (83% adenocarcinoma) received flu vaccine within 65 days of initiating an anti-PD-1 agent (93% nivolumab). Within this cohort, 14 (14%) experienced an IRAE (any grade), including 4% grade 3; no grade 4 or 5 IRAEs were observed. IRAEs were managed with steroids (60% of IRAE cases), treatment interruption (53%), or supportive medications (47%). Phase 3 clinical trials of lung cancer patients treated with pembrolizumab or nivolumab report an incidence of grade 3–4 IRAEs of 7%–26.6% (Supplementary Table).

Laboratory-confirmed Cases of Influenza in the Study Cohort

No cases of laboratory-confirmed influenza occurred among patients who received influenza vaccination and ICI during the 2014–2015 or 2015–2016 seasons. In the 2016–2017 cohort ($n = 197$), 2 cases of influenza A (both H3N2 infections) were diagnosed among 36 patients who presented with 46 episodes of ILI >2 weeks after vaccination. The overall combined incidence of laboratory-confirmed influenza among individuals tested across the 3 seasons was 3.5% (2/56) for the study cohort;

Figure 2. Swimmer's plot. Time (days) from receipt of vaccine and immune checkpoint inhibitor (ICI; immunotherapy) to immune-related adverse event for the 75 patients who experienced these events.

the institution-wide incidence during the same time was 10.7% (925/8617). Incidence was similar across the 3 seasons (range, 9.9%–11.3%). No postvaccination events or exaggerated

local site reactions attributable to influenza vaccination were observed among the study cohort.

DISCUSSION

In our study of 370 cancer patients on ICI who received the inactivated influenza vaccine within 2 months of treatment, the proportion of patients who experienced any new onset IRAE or severe IRAE was not higher than in previously published reports, which were not limited to, and likely included few, patients vaccinated for influenza during or shortly before ICI treatment. The 2 key findings of our study are that no cases of encephalitis, myocarditis, or other grade 5 events occurred in any subgroup of vaccinated patients on ICIs and that the proportion of patients who developed IRAEs in this cohort of patients newly treated with anti-PD-1 agents was lower than reported in published clinical trials, especially lung cancer, which accounted for the largest subset in our study. Specifically, the all-grades and grade-3/4 IRAE rates for flu vaccinated patients on anti-PD-1 agents in our study were 17% and 6.6%, respectively. This is comparable or better than rates reported in published studies of lung cancer, with grade 3/4 IRAE rates typically <20% (Supplementary Table).

Our findings are in contrast with the recent report from Switzerland by Läubli et al [15] who described an overall IRAE

Figure 3. Product-limit survival estimates showing probability of not having an IRAE after having received both immunotherapy and influenza vaccination for patients treated with anti-PD-1 therapy only. Patients who received influenza vaccination and began immunotherapy on the same day are represented in red. Patients who were vaccinated up to 65 days to beginning immunotherapy are represented in green. Patients who were vaccinated within 65 days after beginning immunotherapy are represented in blue. Tests for equality over strata: log-rank $\chi^2 = 1.0$, $P = .6$; Wilcoxon $\chi^2 = 0.8$, $P = .9$. $N = 170$. Abbreviation: IRAE, immune-related adverse event.

rate of 52.2% in individuals on anti-PD-1 therapy vaccinated against influenza over a single season ($n = 23$; 22/23 treated with nivolumab). Of these 23 recipients, 6 (26.1%) had grade 3/4 events, including 2 cases of encephalitis and a single case of autoimmune peripheral neuropathy. The reason for the differences in IRAE rates compared to those from our study is not clear, and the higher incidence has not been reported from any other center. In another small study from the Mayo Clinic, vaccinated and unvaccinated patients on anti-PD-1 therapy did not show any difference in IRAE rates [16].

The other notable finding in our study is the low overall rate of influenza among vaccinated patients on ICIs (3.5%) when compared to rates of laboratory-confirmed influenza (10.7%) at the study institution. Due to our study design, this finding is subject to ascertainment bias and is based on a small number of laboratory-confirmed events. Although no definite conclusions can be drawn, the potential role of anti-PD-1 agents in enhancing vaccine-induced protection merits further investigation in larger epidemiological studies.

The current study has several limitations, including the fact that it is based on retrospective chart review of patients who received flu vaccine at the study institution. We were unable to directly compare risk of IRAEs in vaccinated vs unvaccinated patients because our electronic medical records only capture vaccines administered at the study institution. Since flu vaccine can be obtained in the community, we were not able to establish a reliable cohort of unvaccinated patients on ICIs. This introduces selection bias (patients who begin therapy and do not experience early IRAEs may be more likely to continue therapy and receive vaccination) and healthy user bias (patients who are healthier may be more likely to receive the flu vaccine), both potential factors that explain low IRAE rates in our cohort. In addition, lower-grade IRAEs may not have been captured due to poor clinical documentation, especially relevant to the low occurrence of IRAEs in the ipilimumab plus nivolumab group (30%) in our cohort.

Further, we only report IRAEs that occurred after influenza vaccination and focused on grade 3 or higher, as the goal of the study was to measure incident events potentially triggered by the flu vaccine. Grade 1 or 2 IRAEs that occurred early may not have been adequately documented, leading to lower overall IRAE rates. To address this limitation, we performed a subset analysis of patients on anti-PD-1 agents who received the first dose during the study period and within 65 days of receiving the vaccine. The overall risk of IRAEs was not higher in this subgroup, and no significant effect of order of administration on probability of developing an IRAE was detected (Figures 1 and 3). Although our study is the largest to describe IRAEs in vaccinated patients, there was considerable heterogeneity in the study cohort related to clinical and treatment variables. No systematic approach was followed for flu to determine which patients should receive flu vaccination. Last, our study is entirely observational. Histologic and antigenic characteristics of the tumors, potential cross-reactivity with viral antigens, and

the gut microbiome are possibly important influencing factors but were not specifically explored.

In summary, whether flu vaccination is safe in cancer patients undergoing immunotherapy has become a substantial clinical concern. Immune complications from influenza are rare, and in the general population have been reported to occur more frequently after influenza infection than vaccination. Our data do not indicate an increase in incidence or severity of new onset IRAEs in patients on ICIs who receive the seasonal flu vaccine. In vaccinees who were newly treated with anti-PD-1 agents, IRAE rates were not higher than those reported in published reports. Compared to historical studies, there was no apparent increase in incidence or severity of IRAEs among patients on ICIs who received the inactivated influenza vaccine within approximately 2 months of ICI administration. Based on these findings, we support the current ACIP recommendation for annual seasonal influenza vaccination in patients on ICIs.

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

Financial support. This research was funded in part through the National Institutes of Health/National Cancer Institute Cancer Center Support (grant number P30 CA008748).

Potential conflicts of interest. C. R. C. reports personal fees from Lippincott and Foundation Medicine outside the submitted work. M. A. P. reports grants and personal fees from Bristol-Myers Squibb and personal fees from Merck, Aduro, Array BioPharma, Novartis, Incyte, and NewLink Genetics outside the submitted work. J. D. W. reports personal fees from Adaptive biotech, Advaxis, Amgen, Apricity, Array BioPharma, Ascentage Pharma, Astellas, Bayer, Celgene, Chugai, Eli Lilly, F Star, Janssen, Kleo Pharma, Neon Therapeutics, Ono Pharmaceuticals, Polaris Pharma, Polynoma, Psioxus, Puretech, Recepta, Sella Life, Seramatrix, Surface Oncology, Syndax, and Esanex; personal fees and other from Beigene, Elucida, and Linneaus; and grants and personal fees from Bristol Myers Squibb, Genentech, MedImmune, and Merck outside the submitted work. In addition, J. D. W. has a patent Xenogeneic DNA Vaccines with royalties paid to Merial, a patent alphavirus replicon particles expressing TRP2 (pending), a patent Myeloid-derived suppressor cell (MDSC) assay licensed to Seramatrix, a patent newcastle disease viruses for cancer therapy (pending), a patent Engineered Vaccinia Viruses for Cancer Immunotherapy pending, a patent anti-CD40 agonist mAb fused to Monophosphoryl Lipid A (MPL) for cancer therapy pending, a patent CAR+ T cells targeting differentiation antigens as means to treat cancer pending, a patent anti-PD-1 antibody licensed to Agenus, a patent anti-CTLA 4 antibodies licensed to Agenus, and a patent anti-GITR antibodies and methods of use thereof licensed to Agenus/Incyte and co-founder and Shareholder: Potenza Therapeutics; Tizona Pharmaceuticals; and Trieza, Imvq Therapeutics outside the submitted work. All other authors reported no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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