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Immunogenicity of influenza vaccination in patients with cancer

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Abstract

Background—Influenza leads to significant morbidity and mortality in patients with cancer. Patients with cancer receiving chemotherapy may not mount an adequate immune response to the vaccine. We performed this pilot study to evaluate the immunogenicity of influenza vaccination in patients with cancer receiving chemotherapy.

Methods—During the 2011-2012 influenza season, patients undergoing chemotherapy for solid tumors were given trivalent inactivated influenza vaccine either on the day of chemotherapy (schedule A) or a week prior to chemotherapy (schedule B) via a single 0.5 mL injection in the deltoid muscle region. This was not a randomized trial. Hemagglutination inhibition assays were performed on blood samples from these patients taken at baseline, and 4 weeks post-vaccination. Seroconversion rate (greater than 4-fold increase in titres) and seroprotection rates (post-vaccination titres of >1:40) were calculated for each vaccine component: influenza A (H1N1), A (H3N2) and B.

Results—A total of 18 patients received influenza vaccination as part of this pilot study. Of these, 8 patients received the vaccine on schedule A and 10 patients received the vaccine on schedule B. Geometric mean titres (GMT) against each strain significantly improved post vaccination for both groups, as measured by Signed-Rank test. Seroconversion to at least 1 strain was observed in 75% of patients on schedule A, and 70% in patients vaccinated on schedule B. Seroprotection to at least 1 strain was observed in 100% of patients in the schedule A group, and 60% of patients vaccinated on schedule B. Seroconversion and seroprotection rates against the three influenza strains were not significantly different between the two groups.

Conclusion—Patients with non-hematological malignancies who are receiving chemotherapy mount an immune response to influenza vaccination. Timing of influenza vaccination in relation to chemotherapy does not appear to matter.

Introduction

Influenza infection is a significant cause of morbidity and mortality, affecting 5-10% of the population of the United States annually, and accounts for an annual mortality rate of 22.2 per 100,000 individuals.¹ It is responsible for 226,000 hospitalizations each year, and an annual economic burden of \$87.1 billion.² People over the age of 65 and those who are immunosuppressed, particularly those with cancer, are especially susceptible.³ Cancer is a disease of the elderly, with the median age at diagnosis being 67 years per statistics reported by Surveillance Epidemiology and End Results (SEER). Influenza infection leads to delays and interruption of chemotherapy and may necessitate hospitalization.^{3,4}

Trivalent inactivated influenza vaccine (IIV3) is the most common vaccine formulation administered.² Memory B and T-cells are formed in the setting of vaccination, which allows the adaptive immune system to respond when challenged with pathogen exposure, in a process that can take up to 2 weeks for healthy patients.⁵ Prospective studies demonstrate the inactivated influenza vaccine to have 70-90% efficacy in preventing influenza infection in healthy young adults when a good match exists between the vaccine and epidemic virus.⁶ The trivalent vaccine is almost universally well tolerated. Transient symptoms may include, but are not limited to, local muscle soreness, myalgias, arthralgias, and fever.⁷ Hemagglutination inhibition is the universally accepted assay for quantifying serological response to the vaccine in the research setting.

Response to vaccination relies on an intact immune system that can produce antibodies in response to antigen exposure. Individuals with cancer, however, often have immune deficiencies as a result of their disease and/or immunosuppressive therapies.³ Misconceptions among both patients and physicians about the benefits of the vaccine in these patients, including concern about safety and side-effect profiles, may hinder timely administration of the vaccine.³ There is prospective evidence to suggest that fewer than 50% of adult patients with cancer undergoing chemotherapy receive the influenza vaccination.^{8,9}

The optimal timing for administration of influenza vaccination in patients with cancer receiving chemotherapy is not clear. Although myelosuppression from chemotherapy is transient, it is unknown whether there would be any long-term effect on lymphoid cells. Newer data investigating humoral responses to influenza vaccination in patients with lymphoma treated with rituximab suggest that therapies which deplete B cells impair patients' ability to achieve protective immunity.¹⁰ It is possible, but unproven, that cumulative effects from repeated cycles of cytotoxic chemotherapy may dampen the response to influenza vaccination. Also, steroid use as premedication around the time of chemotherapy may dampen the immune response, and vaccinating in between chemotherapy cycles may be a better approach. Understanding the appropriate timing of the influenza vaccination in relation to chemotherapy would facilitate optimal protection of patients with

cancer from the morbidity and mortality associated with influenza infection in patients with cancer.

The very few studies that have evaluated seroprotection in response to influenza vaccination in patients with cancer were conducted several years ago.¹¹⁻¹⁴ There have been significant changes in the types and schedules of cytotoxic chemotherapy regimens used in the treatment of cancer over the past two decades. We believe that only a prospective randomized study can systematically address the efficacy of influenza vaccination in patients with cancer using modern day chemotherapy regimens, and the optimal timing of administration of influenza vaccine in relation to chemotherapy. We therefore performed this pilot study to determine the optimal timing of seasonal influenza vaccination with regard to chemotherapy administration schedule, to provide preliminary data for an adequately powered randomized prospective study.

Materials and Methods

Study participants

Adult patients (age ≥ 18 years) with non-hematological malignancies receiving cytotoxic chemotherapy in the oncology outpatient clinics at the Alvin J. Siteman Cancer Center, St. Louis, Missouri were invited to participate in this study, during the 2011-2012 influenza season. Institutional review board approval was obtained and subjects provided written informed consent for vaccination and for blood collection for hemagglutination inhibition (HI) assays at baseline and 4 weeks post-vaccination. Patients were eligible if they were receiving cytotoxic chemotherapy either on an every 2 week or 3 week schedule, and individuals receiving weekly chemotherapy were excluded, as were patients receiving radiation therapy. Patients receiving immunotherapy, history of immunosuppression, history of human immunodeficiency virus (HIV) or organ transplantation, chronic steroid therapy (≥ 14 days, though steroids used as part of chemotherapy regimen were allowed) and individuals with absolute lymphocyte count (ALC) less than 1.0 K/cumm were excluded. Patients were also excluded if they had already received the influenza vaccine during that season, or had contra-indications to influenza vaccination such as allergic reaction to influenza vaccine or egg allergies, history of Guillian-Barre syndrome. Patients with active infection or history of influenza-like illness defined as temperature > 37.8°C with cough or sore throat during the present influenza season were excluded.

Study design

The 2011-2012 seasonal influenza vaccine formulation contained A/California/7/2009 (H1N1-like virus); A/Perth/16/2009 (H3N2-like virus); and B/Brisbane/60-2008-like antigens. Seasonal trivalent influenza vaccine was administered as a single 0.5mL intramuscular injection, in the deltoid muscle region. Patients alternated between Schedule A (influenza vaccination on Day 1 of chemotherapy) or schedule B (influenza vaccination one week before chemotherapy). A 10mL blood sample was obtained in a red top tube (without additives) from participants at baseline (prior to vaccination) and 4 weeks post-vaccination at the time of a regular follow-up visit.

Immunogenicity assessment

The samples were sent to Saint Louis Center for Vaccine Development, St. Louis, Missouri. Prevacination susceptibility and post-vaccination serological responses were assessed by hemagglutination inhibition (HI) assay. Seroprotection (HI antibody titers post-vaccination 1:40) and seroconversion (a fourfold rise in titers from prior to vaccination) were used as measures of protective immunity. Reciprocal HI titers of ≥ 40 were considered protective, corresponding to an approximately 50% decrease in influenza infection risk. Geometric mean titres (GMT) for the HI assay at baseline and at 4 weeks were also calculated.

Statistical analysis

As a pilot study, the data analysis was descriptive in nature. Demographic and clinical characteristics of the sample were summarized using descriptive statistics. The differences in seroprotection rates and seroconversion rates between the two groups were summarized using contingency tables and compared by Fisher's exact test. The changes in the HI assay from baseline to 4 weeks as well as the differences between groups were also compared using non-parametric Signed-Rank test and Mann-Whitney Rank-sum test respectively. All the analyses were performed using SAS 9.2 (SAS Institutes, Cary, NC).

Results

Demographics

A total of 42 patients with solid tumors scheduled to receive chemotherapy were consented for this study between September 29, 2011 and November 14, 2011. We excluded 14 patients due to low ALC, one patient was ineligible due to chronic steroid use, an additional patient was ineligible due to chemotherapy being delayed for non-protocol reasons, and two patients withdrew consent. An additional 5 patients were excluded from this study as paired blood samples (baseline and 4 weeks post-vaccination) were not available. This left 18 patients who met all eligibility criteria, were registered to the study and included in the final analysis for this study. Eight patients were vaccinated on schedule A, while 10 patients were vaccinated on schedule B. Baseline and 4 weeks post-vaccination blood samples were collected from all 18 participants. Table 1 describes the demographics of the study subjects. The median age of participants was 56.8 years (range 42.5 to 70.6 years), most were of Caucasian race (13/18) and half of the participants were of male gender (9/18). Seven participants had pancreatic cancer, one had liver cancer, 5 had colorectal cancer, 4 had lung cancer, and 1 patient had sarcoma. All patients enrolled in this study had received prior chemotherapy, with a median of 3 cycles of prior chemotherapy (range 1-12 cycles). Table 1 describes the specific chemotherapy regimens they had received.

Overall Immunogenicity of influenza vaccine—Seroconversion against the H1N1, H3N2 and B strains was observed in 55.5% (10/18), 61.1% (11/18) and 50% (9/18) of patients, respectively. Prior to vaccination, 33.3% (6/18) patients demonstrated seroprotection against any 1 strain, but none of them showed seroprotection to 2 or more strains. Specifically, 0% (0/18), 11.1% (2/18) and 22.2% (4/18) of patients had seroprotective antibody titres ($\geq 1:40$) against H1N1, H3N2 and B respectively. Following

vaccination, seroprotective antibody titres were observed, respectively, in 33.3% (6/18), 44.4% (8/18) and 50% (9/18) of patients against H1N1, H3N2 and B.

Immunogenicity in relation to timing of chemotherapy—Seroconversion to at least 1 strain was observed in 75% (6/8) of patients vaccinated on schedule A, and 70% (7/10) of patients vaccinated on schedule B. Seroconversion to all 3 strains was observed in only 25% (2/8) and 40% (4/10) of patients, respectively. Seroconversion against H1N1, H3N2 and B strains was observed in 63% (5/8), 50% (4/8) and 38% (3/8) of participants vaccinated on schedule A, and 50% (5/10), 70% (7/10) and 60% (6/10) on schedule B (table 2). There was no statistically significant difference in seroconversion rates among patients vaccinated on the two schedules for any of the 3 influenza virus strains, based on the Fisher's exact test.

Seroprotection rates were also assessed for groups A and B. All of the patients (8/8) vaccinated on schedule A demonstrated seroprotection to at least 1 strain, compared to 60% (60%) of patients vaccinated on schedule B. Seroprotection rates were 50% for all 3 strains in the schedule A group, and in the schedule B group they were 20% (2/10), 40% (4/10) and 50% (5/10) for strains H1N1, H3N2 and B respectively (see table 3). Geometric mean titres against each strain did significantly improve in patients in both groups following influenza vaccination, based on the Signed-rank test (table 4). However, no significant difference was found in post-vaccination geometric mean titres between Schedules A and B after adjusting the pre-vaccination titres, based on Mann-Whitney U tests (table 3).

Discussion

Our study demonstrates that patients with solid tumors undergoing chemotherapy respond to trivalent influenza vaccination when receiving modern day cytotoxic chemotherapy regimens. Previous studies date back to the 1970s, and included both patients with hematologic malignancies and solid tumors (table 5).^{4,11,15,16} They also differed in respect to time points at which titres were drawn, and most looked at the primary endpoint of seroconversion only.

Seroprotection is a more clinically important endpoint than seroconversion, since even if a patient responds to the vaccine with a 4 fold increase in titres that may still not result in seroprotection (titres of 1:40) if the immune response is not as robust. Seroprotection with titres of 1:40 is generally held as the objective measure of protection against the influenza virus. Anderson and colleagues examined the seroprotection rates in 59 patients with lung cancer who received influenza vaccination, and found a seroprotection rate of 83%.¹² However, only 14 of the patients enrolled on this study had received chemotherapy in the previous month, and therefore these results cannot be generalized to patients receiving chemotherapy.

Our study is unique in several regards. First it specifically examined the immunogenicity of influenza vaccination in patients with non-hematologic solid tumors who are receiving chemotherapy, while previous studies also included patients with cancer that were not receiving chemotherapy, patients with chronic steroid use and patients with low ALC who may not mount a sufficient immune response. Second, endpoints included seroprotection,

which may be more clinically meaningful. Finally, this study examines the question of whether timing of vaccination in regards to chemotherapy administration impacts vaccination response. The only other study that has examined timing of vaccination was performed by Ortals and colleagues at our institution almost 4 decades ago and demonstrated superior seroconversion rates in patients vaccinated in between chemotherapy cycles, rather than on day 1 of chemotherapy.⁴ Their study included patients with both hematologic and non-hematologic malignancies, over a quarter of whom had absolute lymphocyte counts less than 500 cells/mm³. In addition, 30% of these patients were receiving systemic corticosteroids. We purposefully excluded patients with other confounding factors such as absolute lymphocyte count less than 1000 cells/mm³ and immunosuppression from steroids to specifically address the impact of chemotherapy. Our study did not corroborate the findings of improved response to vaccination in patients vaccinated between chemotherapy cycles, possibly due to differences in the study population.

Limitations of our study include a small sample size, which makes it difficult to generalize the findings to all solid tumors, since none of the participants had cancers of the breast, genitourinary tract, central nervous system and melanoma. Furthermore, not all modern chemotherapy regimens in use were represented. Nevertheless, this study serves as pilot data for the design of an adequately powered prospective study, with patients stratified by cancer type and types of chemotherapy regimens.

Timing of influenza vaccination in relation to chemotherapy for these two time points studied does not appear to change the seroconversion and seroprotection rates. Regardless of timing in relation to chemotherapy, patients did mount an immune response to the vaccine. Given the significant morbidity and mortality posed by influenza infection in patients with cancer, the best defense is prevention via vaccination. This should universally be offered promptly to all patients with no contraindication.

Conclusion

Patients with non-hematological malignancies who are receiving chemotherapy mount an immune response to influenza vaccination. Timing of influenza vaccination in relation to chemotherapy does not appear to matter.

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Table 1

Demographics

Patient number	Primary cancer site	Gender	Race	Age (years)	Chemotherapy regimen	Number of Cycles Previously Received	Vaccine timing in relation to chemotherapy
1	Small Cell Lung Cancer	Female	Caucasian	68	Irinotecan	4	Week before
2	Small Cell Lung Cancer	Female	Caucasian	70	Carboplatin + Etoposide	1	Week before
3	Non Small Cell Lung Cancer	Male	Caucasian	69	Pemetrexed	8	Same day
4	Non Small Cell Lung Cancer	Female	Caucasian	53	Carboplatin + Pemetrexed	3	Week before
5	Sarcoma	Male	Caucasian	65	Adriamycin + Palifosfamide	4	Same day
6	Liver	Female	Caucasian	60	Cisplatin + Gemcitabine	8	Week before
7	Pancreas	Male	Caucasian	54	Carboplatin + Etoposide	1	Week before
8	Colorectal	Male	Caucasian	48	FOLFOX + Avastin	11	Same day
9	Colon	Female	African American	49	FOLFIRI	1	Same day
10	Colorectal	Female	African American	53	FOLFOX	12	Same day
11	Rectum	Male	African American	42	FOLFOX	2	Same day
12	Rectum	Male	Caucasian	61	FOLFOX	7	Week before
13	Pancreas	Male	Caucasian	54	capecitabine + irinotecan + oxaliplatin	3	Same day
14	Pancreas	Male	Caucasian	64	gemcitabine + erlotinib	2	Same day
15	Pancreas	Female	Caucasian	68	Gemcitabine + oxaliplatin	2	Week before
16	Pancreas	Female	Caucasian	56	5 FU+Oxaliplatin	3	Week before
17	Pancreas	Male	African American	51	Gemcitabine	2	Week before
18	Pancreas	Female	African American	57	Gemcitabine	9	Week before

Table 2
Seroconversion Rate (greater than 4 fold increase in titres)

Influenza Strain	Schedule A (n=8)	Schedule B (n=10)	P Value (based on Fisher exact test)
A (H1N ₁)	5 (63%)	5 (50%)	P=0.664
A (H3N2)	4 (50%)	7 (70%)	P=0.631
B	3 (38%)	6 (60%)	P=0.637
>4-fold increase in any strain	6 (75%)	7 (70%)	P>0.99
>4-fold increase in 2 strains	4 (50%)	7 (70%)	P=0.631
>4-fold increase in all 3 strains	2 (25%)	4 (40%)	P=0.638

Table 3

Seroprotection Rate(post vaccination titre > 1:40)

Influenza Strain	Schedule A (n=8)		Schedule B (n=10)		P-value*
	Baseline	4 weeks	Baseline	4 weeks	
A (H1N1)	0 (0%)	4 (50%)	0 (0%)	2 (20%)	P=0.335
A (H3N2)	2 (25%)	4 (50%)	0 (0%)	4 (40%)	P=0.523
B	2 (25%)	4 (50%)	2 (20%)	5 (50%)	P=0.751
>1:40 in any strain	4 (50%)	8 (100%)	2 (20%)	6 (60%)	
>1:40 in 2 strains	0 (0%)	4 (50%)	0 (0%)	3 (30%)	
>1:40 in all 3 strains	0 (0%)	0 (0%)	0 (0%)	2 (20%)	

* based on Mann-Whitney U tests for fold-change in titres between Schedules A and B

Table 4

Geometric mean titres (GMT) and standard deviations (SD)

Influenza strain	Schedule A (n=8)			Schedule B (n=10)		
	GMT at baseline	GMT at 4 weeks	Difference in paired titres* (p-value)	GMT at baseline	GMT at 4 weeks	Difference in paired titres* (p-value)
A (H1N1)	12.3±23.3	53.8±212.6	0.031	10.6±17.1	26.0±73.2	0.016
A (H3N2)	14.7±45.8	64.0±308.2	0.063	9.2±12.3	39.4±93.8	0.004
B	17.4±41.4	69.8±342.6	0.031	14.9±42.9	45.3±122.3	0.016

* based on Signed-Rank tests

Table 5
Studies describing serologic response to influenza vaccination in patients with solid tumors

Author and year of publication	Setting	Patient population	N of patients	Influenza season	Time point titres drawn post-vaccination	Seroconversion	Seroprotection	Timing in relation to chemotherapy
Orbals 1977 ⁴	St.Louis, MO, USA	Lymphoreticular neoplasms Solid tumors Controls	21 21 96	Not mentioned	Baseline, 2 weeks and 4 weeks	67% to A/NJ/76 76% to A/NJ/76 90% to A/NJ/76	Not assessed	Randomized to vaccine on same day as chemotherapy, or a week before
Stiver 1977 ¹⁵	Canada	Lymphoreticular Solid (13 had breast cancer) Controls	19 16 27	1975	2-8 weeks	31.8% for H3N236.4% for B 74% for H3N293% for B	Not assessed	Not assessed
Ganz 1978 ¹⁶	Los Angeles, CA, USA	Solid tumors and lymphomas Controls	17 15	1976	2 weeks and 4 weeks	41-47% for each strain 67% for each strain	Not assessed	Not assessed
Shildt 1979 ¹¹	Fort Sam Houston, TX, USA	Solid tumors and lymphoma, including 22 patients with solid tumors receiving chemotherapy			3 and 9 weeks	41-59% for each strain at 3 weeks	32-86% for each strain at 3 weeks	Not assessed, included patients on treatment (chemotherapy or radiation) versus those off
Anderson 1999 ¹²	UK	Lung cancer, only 14 had received chemotherapy in the preceding month	59	1996	4-6 weeks	Not assessed	83%	Not assessed
Brydak 2000 ¹³	Poland	Breast cancer Controls	9 19	1998-1999	Baseline and 1 month	88.8% to one or more strain 100% to one or more strain	44.4% – 88.9% for each strain 63.2% - 94.7% for each strain	Not assessed
Kim 2013 ¹⁴	Korea	Colorectal cancer	40	2009-2011	1-2 months	26.3% - 52.6% for each strain	42.1%-94.7% for each strain	Not assessed
Loulergue 2011 ¹⁷	France	Breast cancer prostate cancer	18 12	2008-2009	21 days	16-28% for each strain	Not assessed	All on day 1 of chemotherapy