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ORIGINAL ARTICLE

Efficacy of influenza vaccine (Fluvax) in cancer patients on treatment: a prospective single arm, open-label study

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Abstract

Purpose Influenza virus infection has significant morbidity and mortality in patients with medical co-morbidities who are also immunosuppressed. The efficacy of the seasonal influenza vaccine has not been well studied in patients receiving chemotherapy. We assessed the efficacy of seasonal influenza vaccine in patients with non-haematological malignancy on active treatment (chemotherapy and targeted therapy).

Methods A prospective single arm, open label study with 53 patients with non-haematological cancers recruited during the 2011 and 2012 influenza seasons. Participants had one dose of 2011/2012 trivalent vaccine containing strains A/California/7/2009(H1N1), A/Perth/16/2009 (H3N2) and B/Brisbane/60/2008 (Fluvax) prior to or in-between treatment cycles. Haemagglutination inhibition antibody (HIA) titres in serum were measured at baseline 3, 6 and 24 weeks.

Primary endpoint: seroconversion rate (SCR) at 3 weeks.

Secondary endpoints:

- late SCR at 6 weeks.
- rate of sustained sero-protection titres (SPR) at 24 weeks.

Seroconversion was defined as postvaccination ≥ 4-fold increase in HIA titre and sero-protection defined as a HIA ≥ 1:40.

Results The SCR at 3 weeks were 35%, 30% and 22.5% to the H1N1, H3N2 and B/Bris strains, respectively. There were no new cases of late SC at 6 weeks or 24 weeks.

The SPR at 3 weeks were 72.5%, 65% and 40%, respectively, to H1N1, H3N2 and B/Bris. The SPR at 24 weeks to H1N1, H3N2 and B/Bris were 40%, 52.5% and 17.5%, respectively.

Conclusions Patients on various solid tumour treatments achieve sero-protection rate congruent with the general population. The sero-protection HIA titres were not sustained at 24 weeks postvaccination.

Keywords Influenza vaccines · Flu vaccines · Anti-neoplastic agents · Drug therapy · Treatment outcome · Neoplasm

Introduction

Influenza virus is amongst the most common human respiratory viruses. Influenza occurs commonly worldwide with seasonal outbreaks which result in significant morbidity and mortality especially in the elderly and immuno-suppressed population. The estimated annual rate of influenza-associated deaths ranged from 1.4 to 16.7 deaths per

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100,000 persons [1]. For Australians aged ≥ 65 years, the annual excess hospitalizations attributable to influenza were 157 (95% CI, 108–207) per 100,000 with annual influenza related mortality estimated at 6.4 (95% CI, 2.6–10.2) per 100,000 and 116 (95% CI, 71–161) per 100,000 for patients between 50 and 64 years and over 65 years, respectively [2]. Influenza vaccination reduces influenza-related hospitalisation by 49–61% in the general population [3].

Patients diagnosed with cancer on chemotherapy have impaired immune responses with an increased risk of morbidity and mortality from influenza and influenza-like illnesses. The recommendation is for this group of patients to be vaccinated annually. The efficacy, timing during treatment cycle and the optimal dosing of the influenza vaccine are still, however, largely unknown. There have been conflicting reports on the immune response for patients on immunosuppressive agents when compared to the general population.

We conducted a single arm, open label study to assess the efficacy of seasonal influenza vaccine in patients with non-haematological malignancy on active treatment (chemotherapy and targeted therapy) to determine the early serological response at 3 weeks and if sero-protective titres persist at 24 weeks (6 months) following vaccination.

Patients and methods

Study design

We conducted a prospective, single arm, single centre open label study in patients with non-haematological malignancies commencing anti-neoplastic treatment or already on treatment at Flinders Medical Centre during the 2011 and 2012 influenza seasons.

The primary objective was to determine the seroconversion rate (SCR) at 3 weeks. Secondary end points were late SCR (at 6 weeks), and sustained sero-protection (SPR) at 24 weeks. SCR was defined as proportion of participants achieving a 4-fold increase in postvaccination haemagglutination-inhibiting antibody (HIA) titres. Sero-protection rate (SPR) was defined as the percentage of individuals with a serum HIA titre ≥ 1:40.

The summary of CPMP/BWP/214/96 [4] Harmonisation of Requirements for Influenza Vaccines guidelines for vaccine licensing includes a seroconversion rate or significant increase in HIA titre > 40% (SCR > 30% if > 60 years) to any strain, mean geometric increase between day 0 and Day 21 > 2.5 and a sero-protection rate > 70% in vaccine testing trial participants (age 18–60). A lower value is accepted for participants > 60 years.

Statistical consideration

Influenza vaccination in normal immunocompetent age-matched populations yields a protective antibody titre response in up to 80% of the adult population in various studies. Assuming a sero-protection rate of 60% or lower in oncology patients (at least 20% lower than the normal population), a sample size of 43 patients gives 80% power (with an alpha of 0.05) to detect this difference between normal population (historical controls) and oncology patients. Allowing an attrition rate of 15%, 53 patients were recruited for this study. Continuous and categorical variables are reported as mean ± standard deviation or n (%), respectively. Standard definitions for geometric mean titre, sero-protection and seroconversion were used per CPMP guideline [4]. Multivariable logistic regression results are reported for sero-protection, adjusting for age, gender, previous vaccination, year of vaccination (2011 vs 2012), chemotherapy regime, time of serological anti-HIA measurement (0, 3, 6 or 24 weeks) and stage of disease. For seroconversion, numbers did not allow for multivariable analysis. All results are reported as odds ratios (OR) with 95% confidence intervals (CI). There was no evidence of model violation as assessed by the Hosmer-Lemeshow goodness-of-fit statistic. A p value less than 0.05 (two-tailed) is deemed to be statistically significant. All analyses were performed with Stata 14.2 (StataCorp, College Station, Texas).

Patients

The inclusion criteria were > 18 years with histologically/cytologically confirmed non-haematological malignancies (solid tumours) that were commencing anti-neoplastic treatment within 2 weeks or already on treatment. Subjects were required to have a life expectancy of ≥ 6 month.

Exclusion criteria were subjects with prior immunisation with influenza vaccine within the past 6 months; known sensitivity to influenza vaccine, eggs, neomycin or polymyxin; previous history of Guillain-Barre Syndrome; fever (> 38.5 °C) at time of administration of the vaccine; patients with prior splenectomy; patients due to receive 1st dose of chemotherapy > 2 weeks from the proposed date of vaccination (these patients were advised to get vaccinated off trial); patients with haematological malignancies, including lymphoma; and history of primary immunodeficiency syndrome or HIV infection.

The study was approved by the Southern Adelaide Local Health Network (SALHN) Ethics Committee and was carried out per the declaration of Helsinki. All patients provided signed informed consent. The study was registered at the trial registry ACTNZR with trial I.D. ACTRN12611000306910.

Vaccination

During the influenza season 2011 and 2012, patients received one dose of 0.5 ml trivalent influenza vaccine (Fluvax, CSL, Parkville, Victoria, Australia) subcutaneously. The vaccination period coincided with the start of a chemotherapy cycle or up to 3–4 days on post treatment commencement. The

Table 1 Patient demographics $N = 53$ (%)

Mean age (years); S.D	58.3 (± 10.5)
Gender	
Female	31 (58.5%)
Male	22 (41.5%)
Tumour type	
Breast	10 (18.9%)
Colo-rectal	19 (35.8%)
Gynae	8 (15.1%)
Lung	8 (15.1%)
others	8 (15.1%)
Treatment intent	
Neoadjuvant	5 (9.4%)
Adjuvant	17 (32.1%)
Palliative	31 (58.5%)
No prior influenza vaccine	20 (37.7%)
No prior radiotherapy	35 (66.0%)
Anti-neoplastic agents	
Platinum	23 (44.0%)
Anthracyclines	8 (15.0%)
Taxanes	14 (26.0%)
Fluoropyrimidine	20 (37.0%)
Antimetabolite	7 (13.2%)
Tyrosine kinase inhibitor	6 (11.0%)
Monoclonal antibody	14 (26.0%)
Frequency of treatment	
3 weekly	31 (59.0%)
2 weekly	12 (22.0%)
1 weekly	10 (7.0%)
Continuous oral	10 (7.0%)

vaccines contained A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2) and B/Brisbane/60/2008 (B/Bris) as per WHO recommendation for that influenza season.

Laboratory investigations

Blood was collected for antibody titration against influenza viruses at baseline, 3 weeks, 6 weeks and 24 weeks. Once collected, blood samples were transferred to the Microbiology Department at Flinders Medical Centre for processing and batched for a subsequent haemagglutination inhibition (HIA) assay as previously described [5]. The titre was expressed as the reciprocal of the highest serum dilution inhibiting haemagglutination. Serum was assayed for responses against each of the three vaccine strains.

Results

A total of 66 patients undergoing chemotherapy were assessed for eligibility, 8 declined to participate; 4 were ineligible, whilst one patient was vaccinated through her primary care physician. Fifty-three patients were enrolled in this study over two influenza seasons (27 patients in 2011 and 26 patients in 2012). One study participant was treated with R-CHOP for a haematological malignancy and was excluded from the final analysis. The mean age was 58.3 years. Other patient demographic characteristics are shown in Table 1.

The primary endpoint of SCR at 3 weeks (Table 2) was 35%, 30% and 22.5% to the H1N1, H3N2 and B/Bris strains, respectively. There were no new cases of late SCR at 6 weeks or 24 weeks. At baseline, 50% participants demonstrated protective HIA titres, and 11% had protective level titres to all 3 strains prior to vaccination. 3 weeks, postvaccination, SPR was 72.5%, 65.0%, 40.0%, respectively, to the H1N1, H3N2 and B/Bris component of the vaccine. The co-secondary endpoint of sustained SPR at 24 weeks showed a decline in proportion of protective HIA titres (40.0%, 52.5% and 17.5% to H1N1, H3N2 and B/Bris, respectively) (Table 2). SPR to any vaccine component at 24 weeks is 49% depicted in Table 3.

Figure 1 shows the time dependent changes in SPR thru specific time points (baseline, 3, 6 and 24 weeks), with a decline in SPR at 24 weeks.

The time dependent effect in the geometric mean of HIA titre (GMT) for each vaccine strain with the highest GMT recorded at 3 weeks for the H1N1, H3N2 strains and decline at 6 months are shown in Fig. 2. The B/Bris strain had a marginal change in GMT across all time points.

Table 2 SCR and SPR

	*Seroconversion rate** N (%)		*Sero-protection rate #* N (%)	
	3 weeks	6 weeks	3 weeks	24 weeks
A/California/7/2009 (H1N1)	14 (35.0%)	15 (32.6%)	29 (72.5%)	16 (40.0%)
A/Perth/16/2009(H3N2)	12 (30.0%)	12 (26.7%)	25 (65.0%)	21 (52.5%)
B/Brisbane/60/2008	9 (22.5%)	8 (17.7%)	16 (40.0%)	7 (17.5%)

*Missing data: A/Cal; A/Per; B/Bris: 3 weeks- 13; 6 weeks – 8

Missing data: A/Cal; A/Per; B/Bris: 3 weeks- 13; 6 months- 13

Table 3 Summary of immune events

	Baseline	3 weeks	6 weeks	24 weeks
Sero-protection				
Any strain of vaccine	27 (50.0%)	32 (60.3%)	35 (66.0%)	26 (49.0%)
All 3 strains of vaccine	6 (11.0%)	15 (28.3%)	14 (26.4%)	6 (11.3%)

Multivariable regression analysis of predictive factors for response (Table 4) showed that time postvaccination was a significant predictive factor for sero-protection. The multivariate analysis showed a rise in HIA protective titres from baseline for all three strains, which were non-sustained at 24 weeks postvaccination. Other factors such as age, stage of cancer, type of treatment, gender, previous radiation or vaccination were not predictive of sero-protective response. Yukinari Sanada et al. [6] previously demonstrated neutrophil and absolute lymphocyte count were not predictive of immunogenic response.

Discussion

Studies have shown conflicting results on immunogenic responses of influenza vaccination in patients on cancer treatments [7–15]. A review of immunogenic response to influenza vaccine by Gross P.A et al. (1985) [16] showed a heterogenous study population, high rate of type 2 errors and lack of statistical power to determine differences in cancer patients and health cohorts. Sommer et al.'s (2006) [17] review on optimal timing of vaccination in cancer patients also concluded on the limitations of extrapolation of data from older studies due to change in definition of serologic immunogenic response, heterogenous study population and differences in laboratory assay techniques. Some recent publications however have demonstrated that patients on treatment for solid tumours have an immunogenic response and protective HIA titres congruent with or lower than the general population [13, 18, 19].

Our study reports on the immune response to the influenza vaccine in cancer patients vaccinated during active treatment. The study cohort represented different tumour types, with breast, colorectal and gynaecological malignancies predominant; these participants were on different types of cancer treatment regime such as chemotherapy, mono-clonal antibodies, tyrosine kinase inhibitors etc. We excluded a patient treated for a haematological malignancy with anti-CD 20. Haematological patients treated with anti-CD20 monoclonal antibody suppress the humoral response, resulting in a more significant depression of antibody response to vaccination [7] [20].

The early SCR at 3 weeks were 35%, 30% and 22.5% to H1N1, H3N2 and B/Bris strains, respectively, which were lower than the CPMP guidelines for the general population [4] of SCR > 40% (> 30% for > 60 years) in at least one vaccine strain. Though the SCR in our study is lower than expected, some patients on treatment achieved seroconversion level HIA titres. Similarly, P Loulergue et al. [13] showed a low SCR 28% for H1N1, 8% H3N2 and 16% for the B strain in solid tumour patients (breast and prostate) treated with docetaxel. However, Saiama N. Waqar et al. [18] demonstrated a seroconversion rate of 55.5% (10/18), 61.1% (11/18) and 50% (9/18) in H1N1, H3N2 and B strains, respectively, in line with CPMP guidelines for the general population. Our study was designed to detect a difference in SCR between our study cohort and historical controls (general population). Other factors that could account for a lower SCR in our study could be

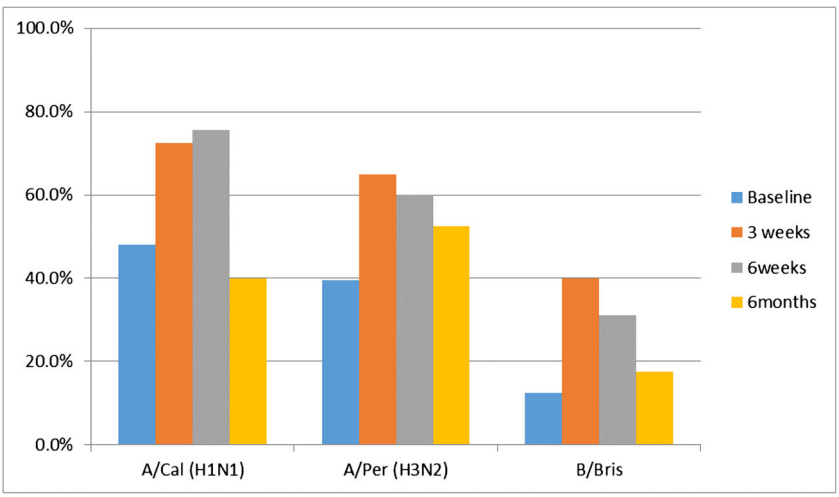

Fig. 1 Histogram of sero-protection rates at different time points

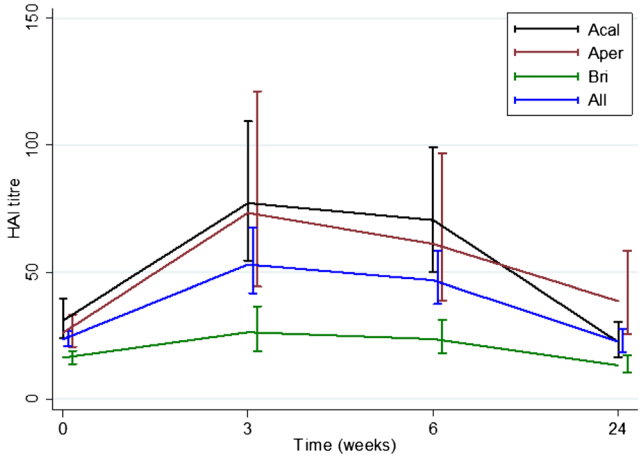

Fig. 2 Geometric mean of HAI titre for each vaccine strain

due to non-exclusion of patients on chronic steroids and missing early SCR data in 24% of our participants. In addition, we also demonstrated the absence of new cases of seroconversion titres 6 weeks postvaccination, a hypothetical time point which could be tested in larger studies exploring the two-dose flu vaccination strategy, an attempt to boost immunogenic responses.

The SPR is a more clinically meaningful endpoint; an HIA titre of ≥ 1:40 reduces the risk of influenza infection by 50% [3]. The CPMP guidelines recommends [4] SPR in at least one strain in > 70% (or > 60% if > 60 years) postvaccination for determination of vaccine efficacy. The SPR at 3 weeks in our cohort was 72.5%, 65.0% and 40.0%, respectively, to the H1N1, H3N2 and B/Bris which shows a protective level immunogenic response. The SPR to the B strain is lower, the reason for this is not entirely clear from our study. Other studies [18, 19] have shown similarly lower immunogenic response in the B strain. The timing of vaccine administration during chemotherapy remains a contentious issue; some studies suggest the timing of vaccine administration in a chemotherapy cycle could play a major role in immune response [8, 21, 22]. The timing for vaccination in this study was based on consensus opinion to vaccinate at a time point furthest away from the next chemotherapy cycle [23]. Bhumsuk Keam et al. [24] demonstrated timing of vaccination on day 1 or day 11 (mid-cycle) has no significant influence on immunogenic response.

Our study is unique in demonstrating the decline in HIA titre at 24 weeks postvaccination, which corresponds to the end of the influenza season. A statistically significant decline in sero-protection HIA titres was also demonstrated by Yukinari Sanada et al. [25] in a study evaluating the immunogenic response to a booster dose in non-responding solid and haematological malignancies. We have also demonstrated the

Table 4 Multi-variable analysis of predictive factors on sero-protection

	A/Cal *OR (95% CI)*	A/Per *OR (95% CI)*	BBris *OR (95% CI)*
Age over 65[a]	0.22 (0.17, 2.82)	1.05 (0.18, 6.26)	1.40 (0.12, 16.29)
Female gender	0.50 (0.12,2.05)	0.51 (0.13, 2.04)	0.57 (0.07, 4.84)
RT	2.13 (0.22, 20.60)	1.01 (0.20, 4.99)	2.09 (0.14, 31.06)
Previous vax	1.40 (0.31, 6.27)	1.44 (0.36, 5.80)	0.20 (0.09, 15.59)
Year [b]	1.24 (0.19, 11.98)	0.57 (0.11, 3.08)	0.74 (0.06, 9.31)
Targeted therapy	6.63 (0.91, 48.45)	1.96 (0.31, 12.60)	1.33 (0.02,9.31)
Chemotherapy	3.37 (0.82, 13.83)	4.58 (0.88, 23.85)	5.06 (0.06,9.32)
Time (weeks)			
Baseline	1	1	1
3	*4.74 (1.94,11.53)***	*3.04 (1.36, 6.80)***	*4.91 (1.47,16.42)**
6	*5.54 (1.96,15.64)***	*2.07 (0.91, 4.70)*	*2.69 (0.83,8.75)*
24	*0.59 (0.19, 1.84)*	*1.52 (0.61, 3.79)*	*0.87 (0.26, 2.93)*
Stage			
1 (ref.)	1	1	1
2	--[c]	5.12 (0.29, 91.01)	--[c]
3	3.36 (0.48, 23.40)	1.89 (0.19, 19.08)	1.81 (0.20, 16.26)
4	2.87 (0.52, 15.86)	1.16 (0.13, 10.24)	0.46 (0.05, 4.56)

*$p < 0.05$, **$p < 0.01$

[a] age dichotomised at < 65 vs. ≥ 65 years

[b] 2011 (reference) vs. 2012

[c] empty cell

OR- odds ratio

absence of late seroconversion (6 weeks) after vaccination in our study cohort, a similar result noted by Yukinari Sanada et al. [25]. Our participant cohort is more representative of a community-based oncology unit with various cancer groups on different treatment regimen and cycle durations represented.

The clinical significance of a decline in sero-protective titres before influenza season end, theoretically, could result in an increased risk of influenza. A meta-analysis by Beck R.C et al. [6] demonstrated a comparable rate of influenza like illness in cancer patients and healthy population. Studies comparing rates between patients with cancer and VICT controls showed comparable rates of ILI low pooled odds of failed to demonstrate a confirmatory evidence of higher influenza risk in cancer patients above the general population.

Some limitations of our study include the absence of data on clinical outcome participants who developed laboratory confirmed influenza infection, correlation of influenza risk with decline in sero-protection titres, correlation of immunogenic response with absolute lymphocyte counts and absence of a control arm.

In conclusion, our study suggests that cancer patients currently on treatment produce an immune response to the flu vaccination; the level of immunogenic response is lower than the general population. The more clinically meaningful endpoint of sero-protection was achieved in > 60% of our cohort, congruent with the CPMP guidelines. We also demonstrated a decline in sero-protection titre in cancer patients on treatment; the clinical significance of this finding can be evaluated in a larger study. Other strategies to boost or maintain sero-protective titres beyond the influenza season can also be considered. [9].

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests

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The primary data is the intellectual property of Flinders Centre for Innovation in Cancer Care; the data is available for the journal review (per the trial institution policies) if requested.