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Improved immunogenicity of high-dose influenza vaccine compared to standard-dose influenza vaccine in adult oncology patients younger than 65 years receiving chemotherapy: A pilot randomized clinical trial☆

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ABSTRACT

Purpose: Patients undergoing chemotherapy often fail to develop robust responses to influenza vaccination. Compared to standard-dose influenza vaccine (SD), high-dose influenza vaccine (HD) has shown improved immunogenicity and protection against influenza illness in adults 65 years and older. This study compared the immunogenicity and tolerability of HD to SD in adults younger than 65 years of age receiving chemotherapy.

Methods: This double-blind study randomized patients receiving chemotherapy to vaccination with either SD or HD influenza vaccine. Hemagglutination inhibition assays (HAI) were performed prior to and 4 weeks after vaccination. HAI were summarized as geometric mean titers (GMT), seroconversion rates, and seroprotection rates.

Results: A total of 105 subjects were enrolled in the trial (51 received SD and 54 received HD). Subjects were well matched for demographic and medical conditions. Both vaccines were well tolerated with no SAEs. Of the 100 subjects with evaluable data, seroconversion rates for all 3 influenza antigens & post-vaccination GMTs for H3N2 & B strains were significantly improved with HD compared to SD. Seroprotection was excellent and equivalent in both groups.

Conclusions: Trivalent high-dose influenza vaccine can be safely administered to patients receiving chemotherapy with improved immunogenicity and seroconversion compared to standard-dose vaccine. Post-vaccination seroprotection rates were similar in both groups. A larger study is needed to show clinical benefits with HD in this population.

This study was registered at ClinicalTrials.gov as NCT01666782.

1. Introduction

Influenza remains a major cause of morbidity and mortality in patients with malignancy [1–3]. Although influenza vaccination is an effective means of preventing influenza [4], cancer patients receiving chemotherapy often fail to mount protective antibody titers to vaccination [5]. Recently, an inactivated high-dose influenza vaccine (HD) with four times the standard dose of hemagglutinin (HA) has been shown to significantly increase antibody response in persons over the age of 65 years and to provide 24% greater efficacy against laboratory-confirmed influenza [6,7].

Although currently licensed for use in persons 65 years or older in the United States, HD has not been studied in younger adults receiving chemotherapy. The aim of this study was to compare the

Abbreviations: HD, high-dose influenza vaccine; HA, hemagglutinin; SD, standard-dose influenza vaccine; RGH, Rochester General Hospital; AE, adverse event; NCI, National Cancer Institute; CTC, common toxicity criteria; SAE, serious adverse event; HAI, hemagglutination inhibition; GMT, geometric mean titer; CDC, Centers for Disease Control and Prevention; GM-CSF, granulocyte-macrophage colony-stimulating factor.

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immunogenicity and safety of HD to standard-dose influenza vaccine (SD) in adult cancer patients younger than 65 years of age receiving chemotherapy.

2. Methods

2.1. Study design

This double-blind, randomized, controlled trial enrolled patients over 2 influenza seasons (2012–2013 and 2013–2014) at the Rochester General Hospital (RGH) in Rochester, NY.

The study was approved by the Clinical Investigation Committee of RGH and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice standards. All subjects provided written informed consent. This study was registered at ClinicalTrials.gov as NCT01666782.

2.2. Subjects

Eligible patients were older than 18 and less than 65 years of age receiving chemotherapy for malignancy who had not received influenza vaccine for the present season. Vaccination status was verified in the electronic medical record. Their expected life expectancy had to be more than 3 months, with adequate organ function (absolute neutrophil count >1000/mm^3, platelet count >100,000/μL, creatinine <2 mg/dL, AST and ALT <3 times the upper limit of normal). Patients were excluded if they had a contraindication to influenza vaccine, had undergone stem cell transplant within a year, or were receiving non-myelosuppressive cancer therapy such as single-agent bevacizumab, erlotinib, or immuno/immunochemotherapy (rituximab or ofatumumab) or had received such therapy in the last 6 months.

2.3. Vaccine

Both vaccines were produced in embryonated chicken eggs, inactivated with formaldehyde, and split with a nonionic detergent. Vaccines were provided by Sanofi Pasteur and were the licensed trivalent SD and trivalent HD vaccines (Fluzone® and Fluzone® High-Dose vaccines respectively) for the 2012–2013 (year 1) and 2013–2014 (year 2) influenza seasons. The lot numbers for the study vaccines were UH734AA (SD) and U4498AA (HD) for year 1 and UH895AA (SD), and U4717AA (HD) for year 2. The HD contained 60 μg and the SD contained 15 μg of HA per strain for the included seasonal H1N1, H3N2 and B influenza strains per 0.5-mL dose. The study vaccine was administered intramuscularly via 0.5-mL syringe using standard sterile technique.

2.4. Study procedures

Patients were randomly assigned 1:1 to receive a single dose of either SD or HD on the first day of chemotherapy. Patients were stratified for randomization according to disease type by solid tumor or hematologic malignancy. The study pharmacists randomized patients to HD or SD arms and then prepared study vaccine. The study nurse, patients and physicians were blinded to HD or SD assignment. Clinical assessment was performed at baseline and 4 weeks (±7 days) after vaccination. Information regarding concomitant medications was reviewed; the study allowed for use of supportive care medications.

2.5. Adverse events

Two different grading systems were used for toxicity evaluation. Solicited adverse events (AEs) included local and systemic symptoms. They were categorized as mild, moderate or severe and were captured if they occurred within 7 days of vaccination. Pain was categorized as none (0), mild (1, easily tolerated), moderate (2, discomfort interferes with daily activity), and severe (3, incapacitating). Erythema and swelling were assessed in terms of the diameter of the maximum reaction size, and classified as mild (<2.5 cm), moderate (2.5–5 cm), and severe (>5 cm). Systemic symptoms included fever, headache, and malaise. Fever (oral temperature) was categorized as mild (99.5–100.4 °F), moderate (>100.4–102.2 °F), and severe (>102.2 °F). The other symptoms were considered mild if they were noticeable but did not interfere with daily activities, moderate if they interfered with daily activity, and severe if they prevented daily activities.

Unsolicited AEs were any adverse events not classified as solicited occurring within 28 days of vaccination. They were graded according to National Cancer Institute (NCI) common toxicity criteria v4.0 (NCI CTC v4.0).

Serious adverse events (SAEs) were defined as any untoward medical occurrences that resulted in death, life-threatening events, required hospitalization, resulted in a congenital anomaly/birth defect or any other important medical event and they were captured throughout the study.

2.6. Immunogenicity

Serum samples obtained before and 28 (±7) days after vaccination were assayed for hemagglutination inhibition (HAI) titers by the Global Clinical Immunology laboratory at Sanofi Pasteur, which remained blinded to vaccine assignment.

2.7. Statistical methods and data management

The primary objective of the study was to compare immunogenicity of HD influenza vaccine to the SD influenza vaccine for both years. The secondary objective was to compare the local and systemic adverse effects of HD influenza vaccine to the SD influenza vaccine. The primary endpoint was to compare the post vaccination geometric mean titers (GMTs) in recipients of HD influenza vaccine to recipients of SD influenza vaccine. The secondary endpoints were to compare the seroprotection rate, seroconversion rate and adverse effects of HD influenza vaccine recipients to those of SD influenza vaccine recipients.

The Statistical Package for Social Sciences for Windows, Version 18.0 (SPSS, 18.0, Chicago, Il) and Microsoft Excel were utilized for data analysis. Sample size calculations for 80% power were based on the studies in the literature indicating a 30–50% effect size on GMTs, assuming equal numbers in each group.

Demographic and clinical characteristics of patients were characterized as mean, range, and standard deviation for age and frequencies and percentages for gender, race, type of cancer (solid tumor or hematological malignancy), single or multi-agent chemotherapy, and chemotherapy regimens.

Serological responses were summarized as HAI geometric mean titers (GMTs), seroconversion rates, and seroprotection rates. Seroprotection rate was defined as the percentage of patients with a day – 28 titer of at least 1:40 and seroconversion rate was defined as the percentage of patients with a ≥4-fold increase in HAI titer after vaccination. GMTs for each strain were calculated by log 2 transformation of HAI titers; *t*-tests were performed on the log-transformed titers. Seroconversion and seroprotection rates were evaluated using χ^2; a p-value < 0.05 was considered significant.

3. Results

One hundred five patients were enrolled and vaccinated; 51 received SD and 54 received HD (Fig. 1). Forty-seven subjects (23 SD and 24 HD) were enrolled during year 1 (2012–2013) and 58 (28