ISSN 1021-366X

Assessment of the Serum Antibody Responses and Safety of Influenza Vaccine for Children with Cancer and Other Chronic Diseases

Abstract

Influenza vaccine was administered to children with acute lymphoblastic leukemia (ALL) in the maintenance stage of their chemotherapy. A total of 65 children was studied, 25 children with ALL, 30 with asthma, and 10 healthy children. Their serum antibody responses to three antigens in the influenza vaccine, B/Yamanashi/166/98, A/New Caledonia/20/99 H1N1 and A/Panama/2007/99, were also tested. After receiving a total of two vaccinations one each 2 weeks apart, children with ALL had a significant increase in antibodies against A/Panama/2007/99 antigen ($p<0.05$). The sero-conversion rate and the sero-response rate were in the ranges of 57.1-84.6% and 40-69.2% respectively. Antibody production in children with ALL was weaker than the antibody response of asthmatic children. Antibody response to Panama antigen in the two groups was similarly satisfactory however. Therefore the answer to the question of whether influenza vaccine could be given to children in the maintenance stage of their chemotherapy, is that no significant differences in serum antibody responses were noted in the present study. In summary, influenza vaccine was safe in ALL and asthmatic children and also stimulated adequate serum antibody responses.

Key words: influenza, acute lymphoblastic leukemia (ALL), immune response

Introduction

Due to its frequent antigenic changes, influenza virus has caused several worldwide pandemics. Soon after the swine-influenza in 1976, the Committee on Infectious Diseases of the American Academy of Pediatrics recommended that children with acute lymphoblastic leukemia be given influenza immunization[(1)]. Since then, there have been studies undertaken, with varying findings however, to ascertain whether children with ALL would produce adequate immunity after vaccination. Due to the possibility of adverse reactions and the doubtful efficacy of the vaccines, physicians are inclined not to give the vaccine to these children. The present study was a prospective study. In the study, ALL children were given influenza vaccine and observed for its safety and the immune response to the vaccine.

ALL children undergoing chemotherapy returned to the clinic every month for follow-up and every two months for inductive chemotherapy. Whether the vaccine should be given together with chemotherapy or at a different time was an issue of concern. To understand the impact of chemotherapy on serum immunity and the appropriate time for vaccination, cases were divided into two groups for study. Cases in the first group were given the first vaccination together with the chemotherapy; cases in the second group were given the first vaccination alone, and the second vaccination together with the chemotherapy.

Materials and Methods

65 cases were collected for study, 25 cases with acute lymphoblastic leukemia (ALL), 30 with asthma, and 10 healthy children.

The ALL children were in the maintenance stage of their chemotherapy. They took 6-mercaptopurine every day, methotrexate every week, and induction

by vincristine and prednisolone every two months. These children were randomly placed in two groups. Children in the first group received chemotherapy and the first flu vaccination on the same day, and the second flu vaccination a month later (Figure 1, subgroup 1). Children in the second group had the first flu vaccination alone, and the second flu vaccination together with chemotherapy a month later (Figure 1, subgroup 2).

Children with asthma were vaccinated during the symptom free period. In the two weeks prior to the vaccination, the use of inhaled steroids was suspended.

Healthy children who had never been vaccinated against influenza were given hepatitis A vaccine as controls.

All children with ALL were given two doses of flu vaccine containing three antigens, (A/Panama/2007/99, A/New Caledonia/20/99, and B/Yamanashi/166/98). Of the remaining children, those who were younger than eight years were given two doses of vaccine; those aged eight and above were given one dose. Vaccinations were administered between October 2000 and January 2001.

Determination of Antibodies: Blood was taken for antibody testing prior to each vaccination. Blood was taken again one month after the last vaccination for follow-up of antibody titers. All sera was frozen at -20℃. It was placed in water measuring 56℃ for deactivation and then processed with enzymes before use. Serum antibody was tested by hemagglutinin inhibition (HI) microtiter method. Antibody levels higher than 40 were considered protective. Sero-conversion rate was the increase of serum antibody from prior to vaccination to either equal to or higher than 40 after vaccination. Sero-response rate was an increase of antibody from either equal to or higher than 20 before vaccination to at least four-fold after vaccination.

All adverse reactions such as fever, local pain, influenza-like symptoms, and general malaise within seven days after vaccination were recorded. Cases were interviewed by telephone on the third and seventh days after the vaccination.

Differences in antibodies among the three groups were compared by one-way ANOVA, and tested by Student's test. Chi-square and Fisher's exact test were used to evaluate the sero-conversion rates, sero-response rates and rates of adverse reactions of each group.

Results

Of the 65 children, 55 were given flu vaccination, and 10 were given hepatitis A vaccine as controls. Their serum immune responses were analyzed (Table 1).

The most common adverse reaction occurring within seven days after vaccination among the two groups was noted to be localized pain, appearing on the day of vaccination, and disappearing soon thereafter. Children with ALL showed more symptoms of fatigue and decreased appetite ($p<0.05$).

In the present study, children with asthma were regarded as cases with normal immunity. Their antibody levels before vaccination were similar. Both the asthmatic and the ALL children had antibody production after the flu vaccination. In asthmatic children, the level of antibodies against Yamanashi and New Caledonia, and in ALL children, the level of antibodies against Panama, had significantly increased compared with that of the control group ($p<0.05$) (Table 3).

Before vaccination, 44 to 66.7% of the subjects, and after vaccination, 70 to 90% of them, had protective antibodies (Table 3). The sero-conversion rates of asthmatic children to Yamanashi, New Caledonia and Panama antigens were

83.3%, 90% and 72.7% respectively. The sero-conversion rates of ALL children to the three antigens were 57.1%, 60% and 84.6% respectively. The sero-conversion rate to New Caledonia antigen of asthma children was significantly higher than that of the controls ($p<0.05$) (Table 4). The sero-conversion rate of ALL children to Panama antigen was higher than that of the asthmatic children.

Four weeks after the vaccination, the sero-response rates of asthmatic children to Yamanashi, New Caledonia and Panama antigens were 66.7%, 70% and 63.6% respectively. The sero-response rates of ALL children to these three antigens were 42.9%, 40% and 69.2% respectively. The sero-response rates of asthmatic children to Yamanashi and New Caledonia were significantly high ($p<0.05$)（Table 4）. Both the ALL and the asthma children had similar sero-conversion and sero-response rates to Panama antigen.

The present study further divided the ALL children into two subgroups to investigate the impact of chemotherapy on serum immunity. Both the sero-conversion and sero-response rates in the two subgroups were not significantly different (Table 5).

Discussion

Routine immunization against influenza is administered each year to the elderly aged 65 and above and to patients with chronic diseases. Use of flu vaccine in children is still limited, and literature on this subject is lacking. Children with asthma, heart diseases, chronic lung diseases, cancer and premature birth are often excluded from routine immunizations. The use of flu vaccine on these children is rare. In epidemics, however, these children are considered to belong to the high-risk groups[8-10]. It can be concluded from the present study

that Influenza immunization of children with acute lymphoblastic leukemia is effective and should be considered. The conclusions can be evaluated by assessing three parameters; geometric mean titer, sero-conversion rate and sero-response rate.

Some reports discussed the immune responses of ALL children on chemotherapy to various vaccines. These children were found less immune responsive than normal children to diphtheria, tetanus, polio, hemophilus, and pneumococcus vaccines[11-14]. ALL children had appropriate immune response to chicken pox vaccine[15,16]. Lange et al. postulated that ALL children were capable of responding adequately to flu vaccine[4], though Gross et al. by referring to published data pointed out that after receiving the flu vaccine the antibody production capability of ALL children receiving chemotherapy was lower than that of ALL children who had already terminated chemotherapy[17]. They maintained that the non-statistical difference was due to the small sampling size (4 to 22 patients). In the present study, the number of patients studied was 25 and their immune responses were found to vary according to antigen. The sero-conversion rates of ALL children to Yamanashi and New Caledonia antigens were slightly higher the previously reported 50%, and the sero-conversion rate to the Panama antigen was almost 84.6%[18]. This promising result was probably due to the improved vaccine or the less intensive use of chemotherapy since 1988.

Most ALL children under study received the same chemotherapy. Children in the three groups were of similar ages. The problems of original antigenic sin could thus be avoided[20]. The sero-conversion rate of normal children was 73-85%, close to that of the asthmatic children[21].

The impact of steroids or other chemotherapy drugs on serum immunity was

not noted in the present study. Both the sero-conversion and sero-response rates in the two subgroups were not significantly different. It appeared that vaccination given together with chemotherapy had no effect on antibody production. This observation could be due to the small number of patients in each group or to the fact that chemotherapy of this kind had no effect on antibody production[22].

The main side effects of ALL children to flu vaccine were fatigue and decreased appetite. These reactions were mild and self-limited. No serious adverse reactions were noted.

Many studies have discussed the serum responses of ALL children to flu vaccine after the termination of chemotherapy, but not the serum responses of children receiving chemotherapy[6,23]. From the present study, it can be noted that the serum responses of ALL children on chemotherapy to flu vaccine varied according to the antigens contained in the vaccine. These children produced satisfactory immune responses to certain antigens, similar to normal children. In summary, the flu vaccine is safe and will produce immunity in Taiwanese children with ALL.

Conclusion

1. After vaccination against influenza, both asthmatic and ALL children will produce antibodies.
2. 44 to 66.7% of children already had protective antibodies before vaccination; after vaccination, 70 to 90% of them will have protective antibodies.

Flu vaccine is safe to use in children with cancer and asthma and will stimulate appropriate serum antibody responses. The use of flu vaccine in these children should be considered.

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Figure 1. Influenza Vaccination of ALL Children Before and After Chemotherapy

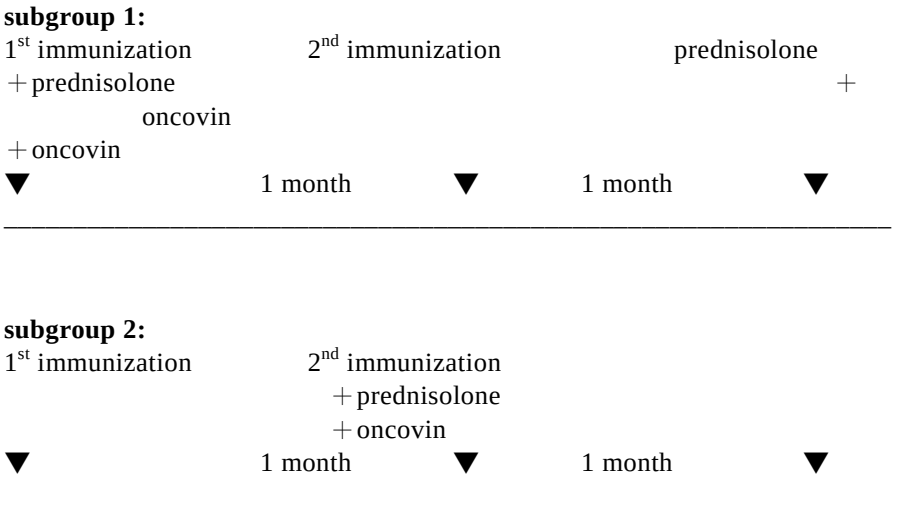

Table 1. Distribution of Acute Lymphoblastic Leukemia, Asthma Children and Controls

	Male	Female	Mean age
ALL	14（56%）	11（44%）	7.3 yr
Asthma	17（57%）	13（43%）	6.5 yr
control	3（30%）	7（70%）	6.1 yr

Table 2. Adverse Reactions to Influenza Vaccine in Children with ALL and Asthma

Type of reaction	ALL（n=25）	Asthma（n=30）
Local	14/25（56%）	18/30（60%）
Malaise	11/25（44%）	3/30（10%）
Decreased appetitie	5/25（20%）	0/30（0%）
Dizzy	3/25（12%）	0/30（0%）
Headache	2/25（8%）	0/30（0%）
Irritability	2/25（8%）	0/30（0%）
Fever	2/25（8%）	5/30（16.7%）

*P<0.05

Table 3. Geometric Mean Titer and Subjects with Protective Titer in 65 Children after Influenza Vaccination

		Geometric mean titer			Log2 GMT			Subjects with protective titer		
		Yamanashi	New caledonia	Panama	Yamanashi	New caledonia	Panama	Yamanashi	New caledonia	Panama
Before Vaccination	L	25.1	39.8	31.6	4.7	5.3	5.0	11/25 （44% ）	15/25 （60% ）	12/25 （48% ）
	A	39.8	50.1	50.1	5.3	5.6	6.9	18/30 （60% ）	20/30 (66.7%)	19/30 (63.3%)
	C	31.6	25.1	63.1	5.0	4.7	5.9	6/10 （60% ）	6/10 （60% ）	9/10 （90% ）
After Vaccination	L	79.4	50.1	125.9*	6.3	5.6	6.9	18/25 （72% ）	17/25 （68% ）	22/25 （88% ）
	A	199.5*	631*	158.5	7.6	9.2*	7.3	27/30 （90% ）	29/30 (96.7%)	27/30 （90% ）
	C	39.8	25.1	63.1	5.3	4.7	5.9	6/10 （60% ）	6/10 （60% ）	6/10 （90% ）

L：acute lymphoblastic leukemia, A：asthma, C：control group

*: $P<0.05$

Table 4. Seroconversion Rate and Seroresponse Rate in 65 Children after Influenza Vaccination

		Seroconversion rate			Seroresponse rate		
		Yamanashi	New caledonia	Panama	Yamanashi	New caledonia	Panama
After Vaccination	L	8/14 (57.1%)	6/10 (60%)	11/13 (84.6%)	8/14 (42.9%)	4/10 (40%)	9/13 (69.2%)
	A	10/12 (83.3%)	9/10 (90%)*	8/11 (72.7%)	8/12 (66.7%)	7/10 (70%)*	7/11 (63.3%)
	C	1/4 (25%)	0/4 (0%)	0/1 (0%)	0/4 (0%)	0/4 (0%)	0/1 (0%)

Table 5. Seroconversion Rate and Seroresponse Rate of Children with ALL in Subgroups 1 and 2

	Seroconversion rate						Seroresponse rate					
Vaccine strain	Yamanashi		New caledonia		Panama		Yamanashi		New caledonia		Panama	
	First dose	Second dose	First dose	Second dose	First dose	Second dose	First dose	Second dose	First dose	Second dose	First dose	Second dose
Subgroup 1 (n=14)	5/9 (55.6%)	5/9 (55.6%)	2/7 (28.6%)	5/7 (71.4%)	6/7 (85.7%)	6/7 (85.7%)	4/9 (44.4%)	4/9 (44.4%)	2/7 (28.6%)	3/7 (42.9%)	5/7 (71.4%)	5/7 (71.4%)
Subgroup 2 (n=11)	3/5 (60%)	3/5 (60%)	0/3 (0%)	1/3 (33.3%)	5/6 (83.3%)	5/6 (83.3%)	1/5 (20%)	2/5 (40%)	0/3 (0%)	1/3 (33.3%)	4/6 (66.7%)	4/6 (66.7%)