Immune Response to 2009 Pandemic H1N1 Influenza Virus A Monovalent Vaccine in Children With Cancer

Ting-Yu Yen, MD,[1,2] Shiann-Tarng Jou, MD, PhD,[1] Yung-Li Yang, MD,[1] Hsiu-Hao Chang, MD,[1] Meng-Yao Lu, MD,[1] Dong-Tsamn Lin, MD,[1] Kai-Hsin Lin, MD,[1] Li-Min Huang, MD, PhD,[1]* and Luan-Yin Chang, MD, PhD[1]*

Purpose. This study investigated the immune response to 2009 pandemic H1N1 influenza monovalent vaccine in children with cancer receiving chemotherapy. ***Methods.*** We enrolled 25 pediatric patients. Ten patients younger than 10 years old received two vaccinations and the remaining 15 patients older than 10 years old received one. We checked hemagglutination-inhibition (HAI) antibody titers in sera of patients before and 3–4 weeks after vaccination. Seroprotective titer was defined as HAI antibody titer $\geq$40 and seroresponse as $\geq$4-fold increase in HAI antibody titers after vaccination. ***Results.*** The pre- and post-vaccination seroprotective rates were 52% and 72% ($P = 0.24$). Sixteen (64%) patients were possibly exposed to 2009 pandemic H1N1 influenza previously, and there was significant association between possible exposure and pre-vaccination seroprotective rate ($P = 0.03$). Post-vaccination seroresponse rate was 32%, and seroresponse was greater in patients without pre-vaccination seroprotective titer than those with pre-vaccination seroprotective titer (50% vs. 15%, $P = 0.07$). Children with lymphocyte counts above 1,500/μl during vaccination period had better seroresponse than those with lymphocyte counts below 1,500/μl ($P = 0.008$). Post-vaccination geometric mean titer (GMT) significantly increased in patients younger than 10 years receiving two vaccinations (pre- and post-vaccination GMT were 21.4 and 60.6, respectively; $P = 0.025$). ***Conclusions.*** Monovalent vaccine for the 2009 pandemic H1N1 influenza A was found to be partially immunogenic in children with cancer, as evidenced by 32% of seroresponse rate. Immune response can be improved with vaccinations administered to patients whose absolute lymphocyte counts returned to a level of 1,500/μl or higher. Pediatr Blood Cancer © 2011 Wiley-Liss, Inc.

Key words: cancer; chemotherapy; children; pandemic H1N1 influenza; vaccine

INTRODUCTION

The pandemic influenza virus A (2009 H1N1), which was first identified on April 2009 in California and in Mexico, has caused significant morbidity and mortality around the world. In most individuals, infection results in influenza-like symptoms and usually runs a benign course [1]; however, in those with comorbidities such as cancer or other chronic diseases, influenza infections can cause serious clinical complications [1–4], including death [5,6]. Prolonged influenza infection or severe influenza-related complications in children being treated for cancer can force an interruption in chemotherapy [7–10], which can increase the risk of death from cancer [9,11]. The primary strategy of preventing such complications is the use of influenza vaccinations.

The American Academy of Pediatrics and the Advisory Committee on Immunization Practices recommends influenza vaccinations for all children 6 months old or older, especially those at high risk of influenza complications (e.g., children with chronic medical conditions such as asthma, diabetes, morbid obesity, immunosuppression, or neurologic disorders) [12,13]. Despite these recommendations, the immunization rate in high-risk children remains low. For example, it has been reported that only about 65–69% of pediatric oncologists routinely recommend yearly influenza vaccinations for children being treated for cancer [14]. They may be reluctant to prescribe such a vaccination because research has not found conclusive evidence regarding the effectiveness of influenza immunization in children with cancer. Some studies have reported adequate responses [15–23] but others only revealed limited results [24–31]. In addition, few studies investigated the immune response and safety of monovalent-inactivated vaccine for the pandemic influenza virus A (2009 H1N1) for children with cancer. This prospective study evaluates the immune response and safety of 2009 pandemic influenza virus A (H1N1) monovalent-inactivated vaccine in children receiving chemotherapy for cancer.

DOI 10.1002/pbc.23113
Published online in Wiley Online Library (wileyonlinelibrary.com).

METHODS

Study Design

We enrolled 6-month to 18-year-old children who received chemotherapy for cancer at National Taiwan University Hospital from December 2009 to January 2010. We excluded children with a previous history of monovalent 2009 pandemic influenza A vaccination, confirmed diagnosis of the pandemic influenza A (2009 H1N1) virus infection prior to the vaccination, and past history of allergy to eggs or egg products as well as those who were receiving other vaccines during the study period. The protocol for this study was approved by Institutional Review Board of National Taiwan University Hospital. Written consent was given by parents or guardians of each child.

Vaccine and Schedule

All children were vaccinated with monovalent-inactivated influenza vaccine for 2009 pandemic influenza virus A (A/California/7/2009 (H1N1)v like strain) according to the guidelines of Taiwan's Advisory Committee on Immunization Practices and

[1]Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan; [2]Department of Pediatrics, Children's Hospital, China Medical University & Hospitals, Taichung, Taiwan

Grant sponsor: A1 Program from National Taiwan University Hospital.

Conflict of interest: Nothing to declare.

*Correspondence to: Li-Min Huang, MD, PhD and Luan-Yin Chang, MD, PhD, Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, No. 8, Chung-Shan South Road, Taipei 10016, Taiwan.
E-mail: lmhuang@ntu.edu.tw; ly7077@tpts6.seed.net.tw; lychang@ntu.edu.tw

Received 11 October 2010; Accepted 8 February 2011

recommendations by the World Health Organization. Children over 1-year-old received one of monovalent-inactivated influenza vaccine for 2009 pandemic influenza virus A (AdimFlu-S, Adimmune, Taichung, Taiwan) and those between 6 and 12 months old received another monovalent-inactivated influenza vaccine for 2009 pandemic influenza virus A (Focetria, Novartis, Basel, Switzerland).

All children received the vaccine intramuscularly. Children <36 months received the vaccine in two doses (0.25 ml with 7.5 μg of hemaglutinin antigen) administered 3–4 weeks apart. Children 36 months old to 10 years old received two doses (0.5 ml with 15 μg of hemaglutinin antigen) 3–4 weeks apart. Children over 10 years old received one dose (0.5 ml).

Sample Collection and Serological Analysis

Once informed consent had been given, we took a 3 ml blood sample from each participant via peripheral vein before they were vaccinated and took another 3–4 weeks afterwards. Blood was centrifuged to separate serum, which was immediately frozen and stored at −80°C until laboratory measurement of hemagglutination-inhibition (HAI) antibody titers to the 2009 pandemic H1N1. All paired sera were tested in duplicate on the same day using identical reagents. Seroprotective was defined as having a HAI antibody titer ≥40 and seroresponse was defined as having a fourfold or greater increase in HAI antibody titers post-vaccination.

Adverse Reactions and Medical Conditions

We collected each patient's demographic data, laboratory data and basic characteristics for the year before he or she was enrolled in the study. We checked complete blood cell count of all the patients just before vaccination of 2009 pandemic H1N1 influenza. Then, they received complete blood cell count follow-up at least once every other week till the end of final blood collection for HAI titer. The vaccination follow-up period was defined as the period from vaccination to the final blood collection for serologic study. Neutropenia was defined as having an absolute neutrophil count <1,500/μl, and lymphopenia as having absolute lymphocyte count <1,500/μl. We monitored possible vaccine-related adverse events by telephone follow-up or by checking a diary kept by the parents, who were requested to record daily body temperatures and any local or systemic reactions for 7 days after each vaccination.

Statistical Analysis

Results were measured in geometric mean titers (GMTs). Immune responses were log transformed. Pre- and post-vaccination (paired samples) comparisons were analyzed using the Wilcoxon-signed ranks test. Comparisons of proportions were analyzed by Fisher's exact test or Mantel–Haenszel chi-square test. A *P*-value below 0.05 was considered significant. All statistical operations were performed using Statistical Package for Social Sciences (SPSS version 16.0).

RESULTS

Demographic Characteristics

Twenty-five cancer patients (19 males and 6 females) completed the study. Their mean age was 10.3 ± 4.8 years (median 11.3 years; range 0.5–17.8 years). The underlying diseases were leukemia (11 patients), lymphoma (4), solid cancer (9), and severe aplastic anemia (1). Ten patients were younger than 10 years old and received two vaccinations; the remaining 15 were older than 10 years and received one vaccination. All 25 patients received chemotherapy within 6 months before enrolled to the study. Twenty-one (84%) of the 25 patients had received chemotherapy within 1 month before vaccination, and 16 (64%) continued to receive the scheduled chemotherapy after the vaccination. At the time of vaccination, 9 patients were found to have neutropenia and 18 had lymphopenia. During the vaccination follow-up period, 17 patients had experienced at least one neutropenia episode, and 22 patients ever had lymphopenia episodes.

Seroprotective and Seroresponse Rates

As shown in Table I, which summarizes the pre-vaccination seroprotective, post-vaccination seroprotective, and seroresponse rates, we found no significant differences between pre- and post-vaccination seroprotective rates. The numbers of children with pre-vaccination seroprotective titers in both age groups were similar [5/10 (50%) and 8/15 (53%) for those younger than 10 years old and those older than 10 years old, respectively, $P = 0.81$].

Because pre-vaccination seroprotective rate was relatively high (52%), we analyzed the possible factors associated with pre-vaccination seroprotective titer are presented in Table II. Sixteen patients had been possibly exposed to the 2009 pandemic H1N1

TABLE I. Pre- and Post-Vaccination Seroprotective Rate and Post-Vaccination Rate in Patients With Cancer Receiving Chemotherapy

	Pre-vaccination (N, %)	Post-vaccination (N, %)	*P*-value[a]
Seroprotective rate			
Age <10 years (N = 10)	5 (50%)	6 (60%)	1
Age ≥10 years (N = 15)	8 (53%)	12 (80%)	0.24
Total (N = 25)	13 (52%)	18 (72%)	0.24
Seroresponse rate			
Age <10 years (N = 10)		4 (40%)	
Age ≥10 years (N = 15)		4 (27%)	
Total (N = 25)		8 (32%)	

N, number. [a]Comparisons of pre- and post-vaccination seroprotective rate patients were performed using Fisher's exact test.

TABLE II. Factors Associated With Pre-Vaccination Seroprotective Titer in Patients With Cancer Receiving Chemotherapy

Factors	Seroprotective (N = 13)	Non-seroprotective (N = 12)	OR (95% CI)	*P*-value[a]
Male	10 (77%)	9 (75%)	1.11 (0.18–6.99)	0.91
Age ≥ 10 years old	8 (62%)	7 (58%)	1.14 (0.23–5.68)	0.87
Previous seasonal influenza vaccine	3 (23%)	3 (25%)	0.90 (0.14–5.65)	0.91
Blood transfusion[b]	8 (62%)	8 (67%)	0.80 (0.16–4.12)	0.79
Possible exposure history[c]	10 (77%)	4 (33%)	6.67 (1.14–38.46)	0.03
Baseline ANC >1,500/μl	8 (62%)	8 (67%)	0.80 (0.16–4.12)	0.79
Baseline ALC >1,500/μl	1 (8%)	5 (42%)	0.25 (0.04–1.69)	0.16
Chemotherapy >30 days[d]	3 (23%)	1 (8%)	3.30 (0.29–37.04)	0.33

N, number; CI, confidence interval; OR, odds ratio; ANC, absolute neutrophil count; ALC, absolute lymphocyte count. [a]Comparisons of seroprotective and non-seroprotective patients were performed using Mantel–Haenszel chi-square test. [b]Received blood component therapy within 1 year before vaccination. [c]Previous possible exposure history to pandemic influenza A (2009 H1N1) virus. [d]The duration between the last chemotherapy and vaccination more than 30 days.

influenza virus prior to the vaccination, and prior exposure was significantly associated with pre-vaccination seroprotective rate ($P = 0.03$). Gender, age, previous seasonal influenza vaccination, blood component therapy, baseline absolute neutrophil count, baseline absolute lymphocyte count, and the timing of last chemotherapy did not predict pre-vaccination seroprotective rate.

The seroresponse rate was 32% in patients receiving chemotherapy (Table I). For those patients without pre-vaccination seroprotective antibody titers, the post-vaccination seroresponse was higher than those patients with pre-vaccination seroprotective antibody titers ≥40 [6/12 (50%) vs. 2/13 (15%), respectively, $P = 0.07$]. Analyzing factors associated with seroresponse (Table III), we found a significant association between having an absolute lymphocyte count of more than 1,500/μl during the vaccination follow-up period and seroresponse ($P = 0.008$). However, we failed to look for the association between seroresponse and absolute lymphocyte count above 1,000/μl or above 500/μl. There was a borderline negative association between pre-vaccination positive seroprotectivity and seroresponse ($P = 0.07$). Other factors, including gender, age, previous seasonal influenza vaccination, blood component therapy, absolute neutrophil count, the timing or the type of chemotherapy, and underlying cancer type were not significantly associated with seroresponse, and this may be limited due to our small sample size.

Table IV shows the pre- and post-vaccination GMT for the 2009 H1N1 influenza virus. In children younger than 10 years old who had received two vaccinations, the post-vaccination GMT was significantly higher than pre-vaccination GMT ($P = 0.025$). However, there was no significant difference between the pre- and post-vaccination GMTs of patients older than 10 years old, who had received only one vaccination ($P = 0.53$).

Adverse Reactions

The parents of all 25 patients completed the diaries reporting possible adverse reactions for 7 days after vaccination. The vaccine was found to be well tolerated in all patients. No patients reported tympanic temperature over 38°C. Only two patients reported mild adverse events, one complaining of a non-painful, non-itching, maculopapular rash 1 day after the vaccination and the other complaining of soreness at the injection site for 2 days.

DISCUSSION

This study is to investigate the efficacy and safety of the monovalent-inactivated vaccine for 2009 pandemic influenza virus A in cancer children receiving current chemotherapy. The vaccine was well tolerated but with limited seroresponse rate (32%), and this was similar to the result of a study for an $ASO3_B$-adjuvanted 2009 pandemic influenza A vaccine in children with cancer [32]. Recent studies have reported that the immune response for influenza in vaccinated children with

TABLE III. Factors Associated With Seroresponse in Patients With Cancer Receiving Chemotherapy

Factors	Seroresponse (N = 8)	Non-seroresponse (N = 17)	OR (95% CI)	*P*-value[a]
Male	5 (63%)	14 (82%)	0.36 (0.05–2.39)	0.29
Age ≥ 10 years old	4 (50%)	11 (65%)	0.55 (0.10–3.00)	0.49
Previous seasonal influenza vaccine	1 (13%)	5 (29%)	0.34 (0.03–3.56)	0.37
Pre-vaccination seroprotective cases	2 (25%)	11 (65%)	0.18 (0.03–1.20)	0.07
Blood transfusion[b]	3 (38%)	7 (58%)	0.86 (0.15–4.81)	0.86
ANC >1,500 cells/μl[c]	4 (50%)	4 (24%)	3.25 (0.55–19.23)	0.19
ALC >1,500 cells/μl[d]	3 (38%)	0 (0%)	NA	0.008
Chemotherapy >30 days[e]	2 (25%)	2 (12%)	2.50 (0.28–22.22)	0.41
Solid tumor	3 (38%)	6 (35%)	1.10 (0.19–6.29)	0.91

N, number; CI, confidence interval; OR, odds ratio; ANC, absolute neutrophil count; ALC, absolute lymphocyte count. [a]*P*-values were from analysis of comparisons of seroresponse and non-seroresponse patients and were performed using Mantel–Haenszel chi-square test. [b]Received blood component therapy after vaccination. [c]ANC maintain more than 1,500 cells/μl during vaccination follow-up period. [d]ALC maintain more than 1,500 cells/μl during vaccination follow-up period. [e]The duration between the last chemotherapy and vaccination more than 30 days.

TABLE IV. Comparison of Pre- and Post-Vaccination GMTs to Both Age Groups (≥10 Years Old and <10 Years Old) Following Vaccination in Patients With Cancer Receiving Chemotherapy

	Pre-vaccination (GMT, 95% CI)	Post-vaccination (GMT, 95% CI)	*P*-value[a]
≥10 years old with one dose vaccine (N = 15)	40.0 (20.6–77.6)	57.9 (34.7–96.5)	0.53
<10 years old with two dose vaccine (N = 10)	21.4 (12.3–37.3)	60.6 (26.2–140.4)	0.025
Total patients (N = 25)	31.2 (19.6–49.5)	59.0 (37.8–92.0)	0.04

N, number; GMT, geometric mean titer; CI, confidence interval. [a]*P*-values were from comparisons of pre- and post-vaccination GMT (paired samples) and were performed using the Wilcoxon-signed rank test.

different malignancies to be weaker than healthy controls [21–23,30,33–35]. While two studies of influenza-immunized children with acute lymphoblastic leukemia reported significant seroconversion [19,20], most of the patients they studied had completed chemotherapy. Three studies have also found that oncology patients who had completed chemotherapy to have better response to influenza vaccine than those actively receiving chemotherapy treatment [25,27,34]. The majority of our patients were still receiving chemotherapy during study period, and the limited seroresponse was expected.

There have been many recommendations regarding the ideal timing of vaccination, including 1 month after completion of chemotherapy, after the peripheral WBC count recovers to a level >1,000/μl [27,36], 2 months after completion of chemotherapy [24], or early in the treatment course for acute lymphocytic leukemia patients [31]. In our study, we could not look for any association between timing of vaccination after completion of chemotherapy and the immune response because most of our patients were still receiving active chemotherapy. Bate et al. [32] reported that lymphopenia (lymphocyte count <1,000/μl) did not influence the seroconversion rate of pandemic (H1N1) 2009 vaccine. However, we did find a significant association between maintaining a lymphocyte count of more than 1,500/μl during vaccination follow-up period and improved seroresponse ($P = 0.008$), suggesting that immunization is best indicated when a patients' absolute lymphocyte count returns to a level higher than 1,500/μl.

Many reports suggest that a two-dose influenza vaccination series produces a better immune response than a one-dose series for oncology patients receiving chemotherapy in a variety of populations and disease types [17,21,23,25,28,34,37,38], though one small but well-designed randomized study failed to show such a difference [39]. In our study, the GMT was found to be significantly increased in patients younger than 10 years, who received two doses of vaccination (pre- and post-vaccination GMT were 21.4 and 60.6, respectively, $P = 0.025$) but there was no significant difference between the pre- and post-vaccination GMTs of patients older than 10 years old, who had received only one vaccination ($P = 0.53$). However, these results should be considered with caution due to the small number of cases we studied in this investigation. Larger studies are needed to confirm such findings before definite recommendations can be made about the number of doses that should be administered to children receiving chemotherapy for cancer.

It is clear that children with cancer have an increased susceptibility to influenza infection [21]. The pre-vaccination seroprotective rate is relatively high (52%, 13/25) in our patients, and it may limit the ability to detect seroresponse. We reviewed the medical history up to 1 year prior to the vaccination and found that 10 of 13 (77%) patients with positive pre-vaccination seroprotective response had possibly been exposed to 2009 pandemic H1N1 influenza virus before they received their vaccinations ($P = 0.03$). For those patients without pre-vaccination seroprotective antibody titers, the post-vaccination seroresponse was 50% (6/12). However, the post-vaccination seroresponse was only 15% (2/13) for those patients with pre-vaccination seroprotective antibody titers ≥40 ($P = 0.07$). This suggests that the primary vaccination seroresponse seems to be better than the booster responses after possibly prior natural infection.

This study has several limitations. First, the study sample size was small. A larger sample size might have shown greater differences between groups. Second, we had no control group in this study, making impossible to confirm comparisons of immune responses to vaccinations in cancer patients and healthy ones. However, our group reported that healthy children had a good seroresponse (about 90%) to the 2009 pandemic H1N1 vaccine [40]. Third, our study group consisted mostly of boys, though gender did not appear to influence immune response to vaccination. Furthermore, we did not administer two-dose vaccinations to children above the age of 10 years old, which might have begun an evaluation of the efficacy of increasing the number of doses to two in older children. Finally, because most of the patients in our study were still receiving chemotherapy during vaccination period, we could not evaluate the immunogenicity of vaccination in patients who had completed the chemotherapy for certain period.

In conclusion, this study found monovalent vaccine for the 2009 pandemic influenza virus A (H1N1) to be well tolerated in children receiving chemotherapy for cancer, but we found immune response in these children to be limited. Vaccinating these children after the absolute lymphocyte count returned to more than 1,500/μl may improve seroresponse, and the seroresponse was greater in patients that did not have pre-vaccination seroprotective titer. Therefore, we suggest that cancer children receiving chemotherapy should receive influenza vaccination as early as possible and we also recommend their household members and hospital staff members to receive annual influenza vaccination to better protect immunocompromised children. Further randomized control trials with larger sample sizes may be performed to test the immunogenicity of vaccination in children with cancer and resolve the questions about the optimal timing and number of doses of the vaccine to achieve better seroresponse.

REFERENCES

1. Launes C, Rives S, Catala A, et al. Pandemic influenza A (2009 H1N1) in children with acute lymphoblastic leukaemia. Br J Haematol 2010;149:874–878.

2. Ramsey CD, Funk D, Miller RR III, et al. Ventilator management for hypoxemic respiratory failure attributable to H1N1 novel swine origin influenza virus. Crit Care Med 2010;38: e58–e65.
3. Rello J, Rodriguez A, Ibanez P, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. Crit Care 2009;13:R148.
4. Redelman-Sidi G, Sepkowitz KA, Huang CK, et al. 2009 H1N1 influenza infection in cancer patients and hematopoietic stem cell transplant recipients. J Infect 2010;60:257–263.
5. van Riel D, den Bakker MA, Leijten LM, et al. Seasonal and pandemic human influenza viruses attach better to human upper respiratory tract epithelium than avian influenza viruses. Am J Pathol 2010;176:1614–1618.
6. Hajjar LA, Mauad T, Galas FR, et al. Severe novel influenza A (H1N1) infection in cancer patients. Ann Oncol 2010;21:2333–2341.
7. Kempe A, Hall CB, MacDonald NE, et al. Influenza in children with cancer. J Pediatr 1989;115:33–39.
8. Feldman S, Webster RG, Sugg M. Influenza in children and young adults with cancer: 20 cases. Cancer 1977;39:350–353.
9. Tasian SK, Park JR, Martin ET, et al. Influenza-associated morbidity in children with cancer. Pediatr Blood Cancer 2008;50:983–987.
10. Caselli D, Carraro F, Castagnola E, et al. Morbidity of pandemic H1N1 influenza in children with cancer. Pediatr Blood Cancer 2010;55:226–228.
11. Potter MN, Foot AB, Oakhill A. Influenza A and the virus associated haemophagocytic syndrome: Cluster of three cases in children with acute leukaemia. J Clin Pathol 1991;44:297–299.
12. Brady MT, Bernstein HH, Byington CL, et al. Policy statement—Recommendations for prevention and control of influenza in children, 2010–2011. Pediatrics. 2010;126:816–826.
13. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep 2010;59:1–62.
14. Porter CC, Poehling KA, Hamilton R, et al. Influenza immunization practices among pediatric oncologists. J Pediatr Hematol Oncol 2003;25:134–138.
15. Lange B, Shapiro SA, Waldman MT, et al. Antibody responses to influenza immunization of children with acute lymphoblastic leukemia. J Infect Dis 1979;140:402–406.
16. Smithson WA, Siem RA, Ritts RE, Jr., et al. Response to influenza virus vaccine in children receiving chemotherapy for malignancy. J Pediatr 1978;93:632–634.
17. Sumaya CV, Williams TE, Brunell PA. Bivalent influenza vaccine in children with cancer. J Infect Dis 1977;136:S656–S660.
18. Ganz PA, Shanley JD, Cherry JD. Responses of patients with neoplastic diseases to influenza virus vaccine. Cancer 1978;42: 2244–2247.
19. Brydak LB, Rokicka-Milewska R, Machala M, et al. Immunogenicity of subunit trivalent influenza vaccine in children with acute lymphoblastic leukemia. Pediatr Infect Dis J 1998;17:125–129.
20. Brydak LB, Rokicka-Milewska R, Jackowska T, et al. Kinetics of humoral response in children with acute lymphoblastic leukemia immunized with influenza vaccine in 1993 in Poland. Leuk Lymphoma 1997;26:163–169.
21. Chisholm JC, Devine T, Charlett A, et al. Response to influenza immunisation during treatment for cancer. Arch Dis Child 2001;84:496–500.
22. Porter CC, Edwards KM, Zhu Y, et al. Immune responses to influenza immunization in children receiving maintenance chemotherapy for acute lymphoblastic leukemia. Pediatr Blood Cancer 2004;42:36–40.
23. Bektas O, Karadeniz C, Oguz A, et al. Assessment of the immune response to trivalent split influenza vaccine in children with solid tumors. Pediatr Blood Cancer 2007;49:914–917.
24. Brown AE, Steinherz PG, Miller DR, et al. Immunization against influenza in children with cancer: Results of a three-dose trial. J Infect Dis 1982;145:126.
25. Steinherz PG, Brown AE, Gross PA, et al. Influenza immunization of children with neoplastic diseases. Cancer 1980;45:750–756.
26. Schafer AI, Churchill WH, Ames P, et al. The influence of chemotherapy on response of patients with hematologic malignancies to influenza vaccine. Cancer 1979;43:25–30.
27. Gross PA, Lee H, Wolff JA, et al. Influenza immunization in immunosuppressed children. J Pediatr 1978;92:30–35.
28. Allison JE, Glezen WP, Taber LH, et al. Reactogenicity and immunogenicity of bivalent influenza A and monovalent influenza B virus vaccines in high-risk children. J Infect Dis 1977; 136:S672–S676.
29. Stiver HG, Weinerman BH. Impaired serum antibody response to inactivated influenza A and B vaccine in cancer patients. Can Med Assoc J 1978;119:733–735, 738.
30. Shahgholi E, Ehsani MA, Salamati P, et al. Immunogenicity of trivalent influenza vaccine in children with acute lymphoblastic leukemia during maintenance therapy. Pediatr Blood Cancer 2010;54:716–720.
31. Reilly A, Kersun LS, McDonald K, et al. The efficacy of influenza vaccination in a pediatric oncology population. J Pediatr Hematol Oncol 2010;32:e177–e181.
32. Bate J, Yung CF, Hoschler K, et al. Immunogenicity of pandemic (H1N1) 2009 vaccine in children with cancer in the United Kingdom. Clin Infect Dis 2010;51:e95–e104.
33. Ring A, Marx G, Steer C, et al. Influenza vaccination and chemotherapy: A shot in the dark? Support Care Cancer 2002;10: 462–465.
34. Matsuzaki A, Suminoe A, Koga Y, et al. Immune response after influenza vaccination in children with cancer. Pediatr Blood Cancer 2005;45:831–837.
35. Chisholm J, Howe K, Taj M, et al. Influenza immunisation in children with solid tumours. Eur J Cancer 2005;41:2280–2287.
36. Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: Measuring disease burden and costs. Vaccine 2007;25:5086–5096.
37. Lo W, Whimbey E, Elting L, et al. Antibody response to a two-dose influenza vaccine regimen in adult lymphoma patients on chemotherapy. Eur J Clin Microbiol Infect Dis 1993;12:778–782.
38. Hsieh YC, Lu MY, Kao CL, et al. Response to influenza vaccine in children with leukemia undergoing chemotherapy. J Formos Med Assoc 2002;101:700–704.
39. Ljungman P, Nahi H, Linde A. Vaccination of patients with haematological malignancies with one or two doses of influenza vaccine: A randomised study. Br J Haematol 2005;130:96–98.
40. Lu CY, Shao PL, Chang LY, et al. Immunogenicity and safety of a monovalent vaccine for the 2009 pandemic influenza virus A (H1N1) in children and adolescents. Vaccine 2010;28:5864–5870.