The Effectiveness of Trivalent Inactivated Influenza Vaccine in Children with Acute Leukemia

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Objective The objective of this study was to determine the effectiveness of trivalent inactivated influenza vaccine (TIV) for the prevention of laboratory-confirmed influenza and influenza-like illnesses (ILI) among children and adolescents receiving therapy for acute leukemia.

Study design A retrospective review of the demographic and clinical characteristics of 498 patients at a pediatric cancer center who received therapy for acute leukemia during 3 successive influenza seasons (2010-2011 through 2012-2013).

Results In 498 patient seasons with a known immunization history (median age, 6 years; range, 1-21), 354 patients (71.1%) were immunized with TIV and 98 (19.7%) received a booster dose of vaccine. Vaccinated and unvaccinated patients had generally similar demographic characteristics. There were no differences in the overall rates of influenza or ILI between vaccinated and unvaccinated patients overall, or in any individual season. There was no difference in the rates of influenza or ILI between patients who received 1 dose of vaccine and those who received 2 doses. Time to first influenza infection and time to first ILI in vaccinated and unvaccinated patients were not different.

Conclusion TIV did not protect children and adolescents with acute leukemia against laboratory-confirmed influenza or ILI. Future prospective studies should assess TIV effectiveness in high-risk subpopulations and alternative strategies to prevent influenza should be considered in this population. *(J Pediatr 2017;191:218-24).*

The Advisory Committee on Immunization Centers for Disease Control and Prevention and the American Academy of Pediatrics recommend all persons 6 months of age and older receive annual seasonal inactivated influenza vaccine, noting that special efforts should be made to vaccinate children who are immunocompromised or who have chronic illnesses, because these patients are at greater risk for complications from influenza than otherwise healthy children.[1-3] Children receiving treatment for cancer have a less robust response to influenza vaccination than do healthy children, but 38%-100% develop immune responses considered to correlate with protection from infection and reported adverse effects associated with these vaccines are generally mild and self-limited.[4,5] Thus, even a small benefit of vaccine has the potential to outweigh risks associated with vaccination. Two systematic reviews conducted in 2013 and 2014, however, concluded that it was uncertain whether or not the immune response to trivalent inactivated influenza vaccine (TIV) protects pediatric or adult oncology patients from influenza or its complications.[4,6] The only study to address this question since the publication of these analyses suggested an overall benefit to pediatric oncology patients, but unclear effectiveness in children with hematologic malignancies.[7] We, therefore, reviewed the vaccination history and clinical course of patients receiving treatment for acute leukemia at a pediatric cancer center over 3 successive influenza seasons. The objectives of this study were to determine the effectiveness of TIV in preventing laboratory confirmed influenza and the influenza-like illnesses (ILI) in patients with acute leukemia.

Methods

St. Jude Children's Research Hospital (St. Jude) provides comprehensive care to approximately 6000 children with cancer and other immunocompromising conditions annually in Memphis, Tennessee, and at a network of 8 domestic affiliates in the United States. Most of these children and adolescents live within the St. Jude catchment area. Children residing near affiliate clinics are referred to St. Jude for enrollment and initial treatment, then may return to the affiliate center for ongoing care closer to home, depending on the intensity of treatment and local resources. Information obtained during all patients' health care encounters at St. Jude and its affiliates is maintained in a centralized electronic health record. Records of patient visits to providers who are not affiliated with St. Jude are also collected. Demographic and clinical characteristics, including respiratory infections and any solicited or

ALC	absolute lymphocyte count
HAI	hemagglutinin inhibition titer
ILI	influenza-like illnesses
TIV	trivalent inactivated influenza vaccine

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unsolicited adverse effects of TIV vaccine, of patients who were undergoing active treatment for acute leukemia during 3 successive influenza seasons (2011-2012, 2012-2013, and 2013-2014) were identified by retrospective review of electronic health records. Yearly influenza seasons were defined as the dates of the first through the last reported cases of influenza in Shelby County, Tennessee, which, in most cases, were inclusive of the dates of reported influenza cases in the counties where affiliates are located. Most influenza infections were confirmed by reverse transcription polymerase chain reaction assays or, less commonly, by rapid influenza antigen detection. ILI were defined using World Health Organization criteria as acute respiratory infections with a measured fever ≥38°C, cough, and onset within the preceding 10 days.[8]

Statistical Analyses

Patient demographic and clinical characteristics and rates of disease were summarized by descriptive statistics. Treatment intensity was stratified as described by Kotecha et al.[7] Overall rates of disease (laboratory-confirmed influenza, the primary endpoint, and ILI, the secondary endpoint) were computed as the total number of cases divided by the total days at risk of infection. Demographic characteristics were compared across influenza season and vaccination status using the Wilcoxon rank sum or Kruskal-Wallis test for continuous variables and the χ^2 or Fisher exact test for categorical variables. The Fisher exact test was used to assess differences in the type of circulating influenza virus across influenza seasons.

In assessing vaccine effectiveness, we assumed that (1) all patients were equally susceptible to influenza, (2) protective antibody responses were present 14 days after administration of TIV, (3) a vaccine did not protect against influenza infection in a subsequent influenza season, and (4) unvaccinated patients remained susceptible to influenza after infection (because multiple types of influenza circulated in each season). Patients were, therefore, considered "immune" 14 days after vaccination, and individuals could, depending on the date they received vaccine, contribute patient-days to both immune and susceptible groups. Rates of disease in immune and susceptible patients were computed as the total number of cases divided by the number of days immune and days susceptible, respectively. Poisson regression was used to compare rates of disease by vaccination status and number of doses of vaccine received. Time to infection was defined as the time between the first day of the influenza season (or cancer therapy, whichever occurred later) and the date of symptom onset; for patients without infections, time to disease was censored at the last day of the influenza season (or completion of cancer therapy, whichever occurred earlier). Kaplan-Meier methods were used to produce time to disease estimates. The log-rank test was used to examine differences in time to first occurrence of disease (influenza or ILI) between susceptible and immune patients within each influenza season and across all influenza seasons.

Logistic regression was used to examine the individual effects of age, sex, treatment intensity, absolute lymphocyte count (ALC), and lymphopenia on the risk of infection among immunized patients. Logistic regression and time to event analyses were conducted under the assumption that patients followed across multiple seasons were independent and multiple infections within the same patient were independent. All analyses were confined to the subset of patients with available vaccination history. SAS version 9.4 (SAS Institute, Cary, North Carolina) was used for all analyses. All statistical tests were 2-sided and $P < .05$ was considered statistically significant.

Results

There were a total of 574 patient influenza seasons; vaccination history was known for 498 patient seasons (86.8%). Most patients with uncertain vaccination status had leukemia diagnosed during the influenza season and lacked documentation of vaccines recently provided by their personal physicians. The demographic and clinical characteristics of the patient population with available vaccination history are summarized in **Table I**. Most patients (94% overall) had acute lymphoblastic leukemia; 93% of these were treated on the TOTALXVI protocol. Patients' age, sex, underlying malignancies, treatment intensity, ALC, and the proportion of patients with mild/moderate or severe lymphopenia were similar across influenza seasons. Most patients (70%) were lymphopenic.

In 498 patient seasons with a known immunization history, 354 patients (71.1%) were vaccinated and 98 (19.7%) received a booster dose of vaccine at a median interval of 35 days (**Table II**). Vaccinated and unvaccinated patients had similar demographic characteristics except that, overall, a greater proportion of patients who were vaccinated had acute lymphoblastic leukemia (95.5% vs 90.3%; $P = .034$) and, overall and across all seasons, vaccinated patients were more likely to be in a low intensity phase of cancer therapy (90.7% vs 73.6% overall; $P < .0001$) than unimmunized patients. There was no association observed between vaccination status or number of doses of vaccine received and risk of developing influenza or ILI. Specifically, there was no difference in the overall rates of influenza between immune and susceptible patients, overall (0.73 vs 0.70; $P = .874$), or in any individual season (2010-2011, 0.86 vs 0.57 [$P = .465$]; 2011-2012, 0.35 vs 0.29 [$P = .784$]; 2012-2013, 1.10 vs 1.62 [$P = .342$]) (**Table II**). There was also no difference in the rates of ILI between immune and susceptible patients, overall (2.44 vs 2.41, $P = .932$), or in any individual season (2010-2011, 2.92 vs 2.70 [$P = .775$]; 2011-2012, 2.27 vs 2.34 [$P = .907$]; 2012-2013, 2.20 vs 2.16 [$P = .967$]).

The rates of influenza and ILI in vaccinated patients receiving 1 or 2 doses of vaccine are summarized for each influenza season and across all seasons in **Table III**. There was no difference in the rates of influenza between patients who received 1 dose and those who received 2 doses, overall (0.60 vs 1.02; $P = .107$), or in any individual season (2010-2011, 0.60 vs 1.53 [$P = .094$]; 2011-2012, 0.29 vs 0.53 [$P = .478$]; 2012-2013, 1.14 vs 1.01 [$P = .798$]). Of patients who received 2 doses, influenza occurred after receiving both doses of vaccine. There was also no difference in the rates of ILI between patients who received 1 dose and those who received 2 doses, overall (2.42