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The Controversy of Varicella Vaccination in Children with Acute Lymphoblastic Leukemia

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Abstract

Background—The available guidelines for varicella vaccination of susceptible children with acute lymphoblastic leukemia (ALL) have become increasingly conservative. However, vaccination of those who have remained in continuous complete remission for one year and are receiving chemotherapy is still considered a reasonable option. There is little available data to allow a comparison of the risk vs. benefit of vaccinating these patients.

Procedure—We retrospectively reviewed mortality due to varicella in the records of 15 pediatric ALL study groups throughout Europe, Asia, and North America during the period 1984–2008.

Results—We found that 20 of 35,128 children with ALL (0.057%; 95% confidence interval [CI], 0.037%–0.088%) died of VZV infection. The mortality rate was lower in North America (3 of

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Conflict of interest statement
No conflict of interest to declare.

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11,558 children, 0.026%; 95% CI, 0.009%–0.076%) than in the Asian countries (2 of 4,882 children, 0.041%; 95% CI, 0.011%–0.149%) and in Europe (15 of 18,688 children, 0.080%; 95% CI, 0.049%–0.132%) consistent with the generally higher rate of VZV vaccination in North America. Fourteen of the 20 patients (70%) died during the first year of treatment for ALL. One death was attributed to varicella vaccination.

Conclusions—The negligible rate of fatal varicella infection in children with ALL, the risk that accompanies vaccination, and the necessity of withholding chemotherapy for vaccination appear to outweigh the potential benefit of varicella vaccination for children during treatment of ALL.

Keywords

varicella zoster virus; pediatric; acute lymphoblastic leukemia; vaccination; immunization; mortality

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy worldwide and is one of the most curable [1–3]. However, children being treated for ALL can experience significant morbidity from varicella zoster virus (VZV) infection, including visceral and central nervous system dissemination, secondary bacterial infection, and post-infectious inflammatory sequelae (e.g., cerebellar ataxia, hematological abnormalities, and glomerulonephritis)[4]. Although primary VZV infection in these children has a mortality rate of 7%–10% in the absence of antiviral treatment, mortality is rare when antivirals and appropriate support are readily available [4,5]. Further, although vaccination is contraindicated until after 1 year of complete remission, such infections are usually more severe during induction or reinduction therapy or during steroid therapy [6].

Official recommendations, such as the Report of the Committee on Infectious Diseases of the American Academy of Pediatrics [AAP] [7,8] and the Canadian Immunization Guide [9], continue to support VZV vaccination for children with ALL, although its risk and potential benefit for these children is controversial. The recently published AAP 2009 recommendation for VZV vaccination is more cautious than its previous 2006 recommendation. The 2006 report [8] recommended that immunization be considered for susceptible children with ALL who have remained in continuous remission for at least 1 year and have a lymphocyte count $>0.7 \times 10^9$/L and a platelet count $>100 \times 10^9$/L. The 2009 report [7] advises against routine immunization and recommends vaccination only with expert guidance and the availability of antiviral therapy. The Canadian Immunization Guide's recommendations [9] are similar to the 2006 recommendations. These recommendations were based on clinical trials showing vaccination to be safe, immunogenic, and effective in children with leukemia who meet the criteria and are at risk of serious disease or death [10–12]. However, in these trials, maintenance chemotherapy was discontinued for one week before and after vaccination, and steroids were discontinued for one week before and two weeks after vaccination. Therefore, the advisability of VZV vaccination of ALL patients, even with the precautions introduced in 2009, remains controversial.

Several factors complicate decisions about whether to vaccinate a pediatric ALL patient against VZV. First, the community prevalence of VZV infection differs geographically, being relatively low in countries where VZV vaccination is universal, such as the United States [13–15], parts of Canada [16], parts of Italy [17], Taiwan [18], and Germany [19]. Second, the risk of serious complications or death from varicella among patients with ALL is poorly defined in the era of effective antiviral therapies. Third, if maintenance therapy is

stopped for vaccination, the risk of ALL relapse may increase [20]. Finally, VZV vaccination has caused serious complications and death in one child with ALL [21]. To evaluate the risks and benefits of VZV vaccination in this group of patients, we reviewed the records of 15 participating pediatric ALL study groups to determine the incidence of death due to VZV infection in children with ALL. The information presented here formed the basis of the 2009 consensus decision of the International Study Group of Childhood ALL (the Ponte di Legno Working Group) that the data do not support immunizing children with ALL against VZV [22].

PATIENTS AND METHODS

Fifteen participating pediatric ALL groups in the regions of Europe (Sweden, Norway, Finland, Denmark, Iceland, the Netherlands, Germany, France, Italy, the Czech Republic, and Israel), Asia (Japan and Taiwan), and North America (the United States and Canada) provided information about all patients who had died of varicella or its complications, within the period 1984 through 2008. The specific time spans reported differed among the groups. For each reported case, the name of the cooperative group and the ALL protocol; the date and the age of the child at diagnosis of ALL; the date of diagnosis of VZV infection; the date of death; the cause of death (whether VZV was a primary or contributing cause of death); and the history of VZV vaccination were provided. The groups were asked whether all patients treated on these protocols had access to diagnosis and appropriate care for VZV and its complications. The following epidemiologic information was also obtained: the cooperative group or center name; the ALL protocol name; the time period of the survey; the number of enrolled patients; and the number of deaths due to varicella. Other information was obtained, the existence of a policy for varicella vaccination in children with cancer; and whether the group or center members were in favor of varicella vaccination for children with ALL.

Statistical Methods

Descriptive statistics were used to summarize the data. Confidence intervals for the incidence of varicella-related death were estimated by using a method adjusted for proportions near zero [23].

RESULTS

The pediatric ALL study groups reported a total of 35,128 children enrolled during various time spans from 1984 through 2008 (Table I). All patients had access to diagnosis and care for VZV infection. Twenty of these children (0.057%; 95% confidence interval [CI], 0.037%–0.088%) died of VZV infection. The mortality rate was lower in North America (3 deaths among 11,558 children [0.026%; 95% CI, 0.009%–0.076%]) than in the Asian (2 deaths among 4,882 children [0.041%; 95% CI, 0.011%–0.149%]) and European (15 deaths among 18,688 children [0.080%; 95% CI, 0.049%–0.132 %]) countries (Table I), consistent with the generally higher rate of VZV vaccination in North America [13;14]. VZV vaccination of children with ALL was not favored by 9 of the 15 cooperative groups that answered the item; of the remaining six groups, five did not answer the question and one answered “don’t know.” In May 2009, after reviewing the data gathered for this study, The International Study Group of Childhood ALL (the Ponte di Legno Working Group) reached a full consensus that the data do not support immunizing children with ALL against VZV [22].

Table II summarizes the characteristics of the 20 children who died of VZV infection. Their median age was 5 years (range, 2–18 years) at the time of death. Seven deaths occurred at the time of diagnosis or during remission induction therapy, 5 during consolidation or

reinduction therapy, 4 during maintenance therapy, 1 six months after completion of therapy, and 1 twenty weeks after allogeneic transplantation. In 6 cases (30%), varicella developed more than 12 months after diagnosis of ALL.

The most frequent complications of varicella among the twenty children who died were hepatitis (8), pneumonia (7), multiple organ failure (6), central nervous system involvement (5), disseminated intravascular coagulation (3), myocarditis (3), renal pathology (2), and pancreatitis (1) (Table 2). Only one child was known to have received VZV immunization, and the fatal infection was attributed to the vaccine [21].

DISCUSSION

The data from this large retrospective study strongly suggest that VZV vaccination should not be undertaken in children with ALL. We found that only 0.057% of children enrolled on ALL protocols during the modern era (after 1984) died of VZV infection. Further, only six of the 20 children who died had had a diagnosis of ALL more than 1 year previously and therefore might have been eligible for vaccination under recent guidelines.

Although broadly informative data are limited, our results confirm that mortality from VZV infection is rare among immunocompromised children with ALL in high-income countries [24], where access to diagnosis and care is ready accessible. The risk of VZV infection is also reduced in countries where susceptible children 1 year and older in the general population are routinely vaccinated [15,25,26]. In the United States, where universal VZV vaccination was introduced in 1995, coverage (one VZV vaccination) was 89% among US children aged 19 to 35 months in 2006 [13] and 75.7% among adolescents aged 13–17 years in 2007 [14]. By contrast, VZV vaccination is targeted to groups at high risk in most European countries [27,28], with the exception of Germany, where VZV vaccination has been recommended since 2004 for all children aged 11–14 months and for susceptible adolescents [19,29]. In Italy, universal VZV vaccination was introduced in 2006 in the Veneto Region for all children aged 14 months and for susceptible adolescents [17]. In France, vaccination is recommended for groups at high risk [28]. In Israel, VZV vaccine has been available since 2000, but vaccination is not government-sponsored [30]. In the Netherlands, VZV vaccination is not recommended. In Japan, VZV vaccine has been available for more than 2 decades for children age ≥1 year; however, vaccination is voluntary and the coverage rate (25%–30%) is insufficient to control epidemics [31]. In Taiwan, VZV vaccine has been available free of charge since 2004 [18], and approximately 95% of children 1 to 2 years of age are immunized (personal communication, Dr. L.Y. Chang, National Taiwan University, Taipei, E-mail: lychang@ntu.edu.tw; 17 June 2009 – Supplemental Appendix I).

VZV vaccination was not embraced as expected by cancer care providers when it became available, despite good seroconversion rates (80%–85% after 1 dose of vaccine and 90% after 2 doses) [32]; the risk of side effects is the most likely reason. Although official recommendations and guidelines [7–9] suggest that individuals with ALL could be vaccinated, pediatric oncologists avoided VZV vaccination to prevent transmission of vaccine-type VZV to susceptible patients [11] and to avoid having to withhold chemotherapy for two weeks. Further, a case of progression to severe VZV disease and death after vaccination was recently reported [21] (this patient is included in our study), although the total number of patients vaccinated is unknown. Moreover, of the 20 fatal cases described here, only 6 occurred more than 12 months after initial diagnosis of ALL and could possibly have been prevented by immunization. Therefore, the benefit of vaccination in preventing fatal varicella appears to be negligible. The rate of early mortality from

infection overall is declining, Prucker et al.[33] reported only 21 infectious deaths, and no deaths from VZV, in a population of 896 children with ALL.

We began our study before publication of the 2009 AAP guidelines [7], which advise that children with ALL should not routinely be immunized where the incidence of VZV infection is decreasing and that immunization should be undertaken only under expert guidance and with the availability of antiviral therapy. We are encouraged by the more cautious content of this recommendation; however, we propose that vaccination of patients with ALL should be avoided entirely. Most of the deaths from VZV identified in this study occurred during the early phases of intensive chemotherapy and would not have been prevented by immunization after one year of remission. In environments that offer ready access to diagnostic tools and treatment and that provide intensive immunosuppressive chemotherapy, as in our study, the benefit of VZV vaccination is likely to be outweighed by the risk of lethal infection with vaccine-type VZV [21] and by the risk of relapsed ALL.

In less affluent ALL treatment settings, such as the Latin American partner sites of St. Jude Children's Research Hospital, the clinical experiences indicate that VZV infection is an important cause of morbidity and mortality due to the higher incidence of varicella among children with cancer and because of inadequate infrastructure and supplies for its prevention, diagnosis, and treatment. Further, VZV vaccination here and in most resource-poor settings is not yet universal. Oncologists at such sites frequently consider preventive VZV vaccination for children with ALL, and they often consult published guidelines [7–9]. However, such children are also vulnerable to the risks of VZV vaccination. Therefore, we suggest that other preventive measures are the best way to minimize the likelihood of VZV infection in these settings: immunization of susceptible health care staff and of patients' household contacts, especially young siblings, and optimization of infection control practices with emphasis on isolation of infected patients. Recently vaccinated household members who experience rash should avoid direct contact with the immunocompromised patient until the rash resolves [7]. Finally, patients' treating physicians should be alert to that VZV infection can present with few or no cutaneous lesions in children with ALL; these patients should initiate appropriate antiviral treatment promptly. Rowland et al. [34] reported that it can present in the form of back pain or abdominal pain, which can be ominous symptoms. Another series described back pain in patients who died of VZV complications [6].

Limitations of this study include its retrospective design and the analysis of VZV mortality but not of rates of VZV infection. While the result of our study is certain, firm recommendations might require additional studies. However, we believe that the potentially fatal complications of vaccination, the risk associated with withholding chemotherapy, the rarity of death from VZV infection in our study after the first year of treatment for ALL, and the negligible overall risk of death from VZV infection in our study suggest that vaccination has no meaningful impact on mortality and hence cannot be recommended on that basis. A case may be made for vaccination after the first year of ALL therapy in settings where the risk of VZV infection is high, but the possible benefit remains uncertain. The most effective practices may be those that focus on herd immunity and/or vaccination of household contacts. Administration of live vaccine is considered acceptable 3–6 months after immunosuppressive cancer chemotherapy has been discontinued and the lymphocyte count is at least 1.5×10^9/L [7,21].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Number of deaths due to varicella infection among 35,128 children with acute lymphoblastic leukemia

	Group	Protocol	Country	Period	No. Patients	No. Deaths
1	AIEOP	91, 95 and 2000	Italy	1991–2008	4934	3
2	SJCRH	Total XI–XV	USA	1984–2007	1512	1
3	INS	INS-1989, 2003	Israel	1989–2007	628	3
4	Czech Rep	95, 2002	Czech Republic	1996–2007	690	0
5	COALL	COALL92-97	Germany	1992–2003	1188	0
6	BFM	ALL-2000	Germany	2000–2008	3500	7
7	JACLS	97 and 02	Japan	1997–2006	1612	1
8	TCCSG	92, 95 and 99	Japan	1992–2003	1698	0
9	KYCCSG	ALL02	Japan	2002–2007	165	1
10	DCOG	8, 9 and 10	The Netherlands	1991–2008	1656	2
11	POG	Various	North America	1990–2005	8746	2
12	NOPHO	ALL-92; ALL-2000	Nordic Countries	1992–2006	2668	0
13	FRALLE	FRALLE 93, 2000 A + BT	France	1993–2008	3424	0
14	TPOG	ALL-97; ALL-2002	Taiwan	1997–2008	1407	0
15	DFCI	DFCIC-Protocol 95	North America	1996–2008	1300	0
	TOTAL				**35,128**	**20**

Abbreviations: AIEOP, Associazione Italiana di Ematologia ed Oncologia Pediatrica; SJCRH, St. Jude Children's Research Hospital; INS, Israel National Studies; COALL, Cooperative Acute Lymphoblastic Leukemia Study Group; BFM, Berlin-Frankfurt-Münster Group; JACLS, Japan Association of Childhood Leukemia Study; TCCSG, Tokyo Children's Cancer Study Group; KYCCSG, Kyushu Yamaguchi Children's Cancer Study Group; DCOG, Dutch Childhood Oncology group; POG, Pediatric Oncology group; NOPHO; Nordic Society for Paediatric Haematology-Oncology; FRALLE, French Acute Lymphoblastic Leukemia Study Group; TPOG, Taiwan Pediatric Oncology Group; DFCI, Dana-Farber Cancer Institute.

Table II

Characteristics of 20 children with acute lymphoblastic leukemia who died of varicella infection

Patient	Age at death (y)	Varicella vaccination	ALL protocol	Treatment phase	ALL status at time of death	Time from diagnosis of ALL to diagnosis of varicella	Days from varicella onset to death	Cause of death
1	9	No	JACLS-97	Induction	AD	27 days	13	Multiple organ failure
2	18	No	INS-89	6 months off therapy	CR	2.5 years	6	Massive hepatic failure and acute respiratory insufficiency
3	5	No	INS 2003	Induction	AD	10 days	5	Pneumonia, hepatitis, disseminated intravascular coagulation, multiple organ failure.
4	4	No	INS 2003	Maintenance	CR	18 months	33	Acute myocarditis
5	13	No	DCOG-9	20 weeks after transplantation	NK	NK	15	Pneumonia
6	6	No	DCOG-10	Maintenance	CR	18 months	38	Pneumonia
7	6	No	KYCCSG 02	Re-induction	CR	5 months	2	Disseminated intravascular coagulation
8	4	NK*	ALL-BFM 2000	Prephase of induction	Before treatment	2 days	3	Pneumonia, pulmonary leukostasis syndrome
9	4	Yes21	ALL-BFM 2000	Re-induction	CR	5 months	13	Hepatitis, encephalitis, multiple organ failure.*
10	3	NK	ALL-BFM 2000	Induction	AD	45 days	22	Hepatitis, encephalitis
11	5	No	ALL-BFM 2000	Maintenance	CR	18 months	6	Pneumonitis, cardio-respiratory failure
12	5	No	ALL-BFM 2000	Re-induction	CR	6 months	3	Hepatitis
13	5	No	ALL-BFM 2000	Induction	AD	15 days	13	Hepatitis, encephalitis, multiple organ failure.
14	4	No	ALL-BFM 2000	Re-induction	CR	6 months	9	Hepatitis, pancreatitis, nephritis, encephalitis
15	4	No	AIEOP ALL2000	At diagnosis of leukemia	Before treatment	0 days	1	Interstitial pneumonia
16	16	No	SJCRH Total XI	Maintenance	CR	7 months	4	Hepatitis, renal failure, pneumonia, DIC
17	2	No	AIEOP ALL91	Induction	AD	26 days	5	Myocarditis, multiple organ failure
18	6	No	AIEOP ALL91	Consolidation	CR	75 days	4	Multiple organ failure, encephalitis, meningitis
19	NK	NK	POG	NK	NK	17 moths	NK	NK
20	NK	NK	POG	NK	NK	17 moths	NK	NK

NK: not known; CR: Complete remission; NA: not applicable; AD: active disease

* Varicella vaccination was introduced in Germany in 2004/2005.