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# Varicella vaccination in children with acute lymphoblastic leukemia: Experience from a pediatric cancer centre in India

Vijay Guru, Venkatraman Radhakrishnan*, Tenali Sagar

*Department of Medical Oncology (Pediatric Oncology Division), Cancer Institute (WIA), Adyar, Chennai, India*

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ABSTRACT

*Background:* Varicella infection in children with Acute Lymphoblastic Leukemia (ALL) is associated with significant morbidity and mortality. Immunisation against varicella infection is not mandatory as per the national immunisation program in India and therefore the majority of children with ALL are unimmunised and are at an increased risk of infection.
*Methods:* The present study retrospectively analysed the case records of patients with ALL diagnosed between January 2013 and May 2017 and received the varicella vaccine. Patients with ALL who had no previous history of varicella infection or immunisation and were in remission were given a single dose of live attenuated varicella vaccine prior to the start of the maintenance phase of treatment.
*Results:* The study included 125 patients with a median age of 6 years and 57% patients were males. Fifty-two patients (41%) developed vaccine-induced varicella. The median time to develop vaccine-induced varicella was 21 days (range: 10–35 days). The median duration of fever was 2 days (range; 1–8) and 5 patients developed febrile neutropenia. Maintenance chemotherapy was withheld in symptomatic patients for a median duration of 7 days (range: 3–15 days). Breakthrough varicella infection after vaccination was seen in 2 patients. There was no mortality due to vaccine-induced varicella.
*Conclusion:* Varicella immunisation is safe and efficacious in children with ALL and should be considered in countries where varicella immunisation is not routinely practiced. Vaccine-induced varicella is commonly seen; however, it is self-limiting.


## 1. Introduction

Varicella (chickenpox) caused by varicella-zoster virus (VZV) is an acute and contagious disease. Immune suppression can lead to severe, prolonged and disseminated varicella, with complications, including pneumonia, hepatitis, encephalitis, and death [1,2]. Untreated varicella has a mortality rate of 7%–10% in children with acute lymphoblastic leukemia (ALL) [3]. Children with ALL who develop varicella can have atypical presentations that can lead to diagnostic delay and thereby increased morbidity [4,5]. In India where routine vaccination against varicella is not a part of the national immunisation schedule, the risk of VZV exposure compromises the lives of many children with ALL on treatment [6]. Passive immunisation and acyclovir prophylaxis can reduce the incidence of severe complications of VZV infection, however, they are expensive and needs coverage of many children exposed to the infection. It is not uncommon for immunocompromised children with varicella presenting late to the hospital usually after complications have occurred.

Routine vaccination against VZV for children with ALL without a history of varicella infection or vaccination in the past was initiated prior to starting their maintenance chemotherapy at our hospital in January 2014. The reason for immunizing children with ALL against VZV at our hospital was the frequent varicella outbreaks involving majority of the children undergoing treatment; leading to treatment interruptions, increased cost of providing prophylaxis to patients and families, increased cost of managing disease morbidity, and mortality in three patients with ALL receiving maintenance chemotherapy who developed disseminated varicella during 2012–2013. The present study was conducted to analyze our

* Corresponding author. Medical and Pediatric Oncology, Cancer Institute (WIA), Adyar, Chennai, Tamilnadu, India.
*E-mail address:* venkymd@gmail.com (V. Radhakrishnan).
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experience with VZV vaccination in children with ALL.

## 2. Patients and methods

The study was conducted retrospectively and included children with ALL who were diagnosed between January 2013 and May 2017 and received the varicella vaccine. Written informed consent was obtained from the parents prior to starting the child's treatment for ALL, the consent also included details of the varicella vaccination. Patients who had no previous history of varicella infection or immunisation and were in remission were given a single dose of live attenuated varicella vaccine (Oka strain, one dose of vaccine contained 1350 plaque forming units). VZV vaccine was given in the delayed intensification phase of treatment, a week after the last dose of cytarabine and if the white blood cell counts were more than 4000/cumm, absolute neutrophil count more than 1500/cumm, absolute lymphocyte count more than 700/cumm and platelets more than 100,000/cumm. Patients received steroids a minimum of 4 weeks prior to the varicella vaccination. Maintenance chemotherapy was started one week after the varicella vaccination. Intrathecal methotrexate was not administered one week before and after the varicella vaccination. All patients were in complete remission at the time of vaccination. Breakthrough varicella was defined as varicella presenting after 6 weeks of vaccination. Clinical data on each patient was obtained from the case records.

## 3. Results

A total of 405 children were diagnosed with ALL at our centre between January 2013 and May 2017 and among these 125/405 (31%) eligible patients were given the varicella vaccine prior to starting their maintenance chemotherapy. The median age was 6 years (range: 1–16 years) and 72/125 (57%) patients were males. Forty-eight out of 125 patients (39%) were immunised against diphtheria, pertussis, tetanus, polio, and measles prior to starting treatment for ALL. Pre-B ALL was the most common immunophenotype observed in 103/125 (83%) patients followed by T-cell ALL in 20 (16%) and bi-phenotypic leukemia in 2 (3%). All patients were treated on a common risk-stratified protocol. According to the risk-stratification, 35/125 (28%) were classified as standard-risk, 41/125 (33%) as intermediate-risk and 49/125 (39%) as high-risk. The median duration from the last dose of chemotherapy to the administration of varicella vaccine was 14 days (range: 7–21 days). Fifty-two of 125 (41%) patients developed vaccine-induced varicella. Fever with maculopapular rash was observed in all patients who developed vaccine-induced varicella. The median time to develop vaccine-induced varicella was 21 days (range: 10–35 days). The median duration of fever was 2 days (range: 1–8 days). Five patients developed febrile neutropenia and were hospitalized and treated with intravenous antibiotics, rest of the patients were treated on an outpatient basis, however, they were segregated from other children attending the outpatient department. Breakthrough varicella after vaccination was observed in 2 patients, one developed after 48 days and the other after 61 days. Unlike the vaccine-induced varicella, patients with breakthrough varicella presented with extensive vesico-papular lesions. All patients with vaccine-induced varicella were treated with acyclovir. Maintenance chemotherapy was withheld in patients with vaccine-induced varicella for a median duration of 7 days (range: 3–15 days). There were no complications seen in these patients and there was no mortality due to vaccine-induced varicella. Since the initiation of varicella vaccination for patients with ALL at our hospital, we have not witnessed any varicella related death.

## 4. Discussion

Vaccination against VZV is not universal in India unlike many high-income countries and therefore the incidence of varicella in the community is high. Immunisation against common vaccine-preventable diseases especially among the poor socio-economic group in India is inadequate as was seen in our study were only 39% patients reported previously being immunised for age as per the national immunisation schedule. However, there could be a recall bias among parents that could be the reason for a lower reported vaccine coverage compared to the national average.

Vaccination against VZV during anti-leukemic therapy has been debated for and against in the literature. A review of published literature by Caniza et al. on vaccinating children with ALL with VZV vaccine concluded that the risks associated with vaccination may be greater than those associated with the acquisition of the infection itself [3]. These recommendations are mainly tailored towards high-income countries where the varicella vaccination is usually universal and therefore there is a high level of herd immunity and lower incidence of varicella infection in the community [3]. Access to high-quality health care resources, varicella immunoglobulin and early detection and treatment of varicella infection in high-income countries makes the routine use of varicella vaccine in patients with ALL questionable. Whether these recommendations are applicable to low-middle income countries is debatable. Poor nutritional status, overcrowding in hospitals and homes, lack of access to VZV immunoglobulin, and delay in presentation to hospital after exposure to or onset of varicella are important determinants of susceptibility and mortality to varicella in low middle income countries [LMIC]. The absence of routine immunisation against varicella in LMIC leads to reduced herd immunity and higher chance patients with leukemia to contact varicella. Untreated varicella vaccine in immunocompromised children is associated with high mortality and morbidity [1]. A single dose of varicella vaccine in this susceptible group of patients in LMIC is not only cost effective but can also reduce mortality.

We used a single dose of vaccine instead of two doses, a month apart, as there is evidence that a single dose is as effective as two doses of the vaccine [7]. Seroconversion rate in children with ALL after a single dose of varicella vaccine has been reported at 85–90% and after 2 doses at 95% [7,8]. However, a study showed that a single dose varicella vaccine was insufficient to provide long-term immunity when compared to two doses [9]. We did not measure the varicella antibody titers post-vaccination. There are concerns that withholding maintenance chemotherapy for one week after varicella vaccination and for a longer duration in children who develop vaccine-induced varicella may be detrimental as it increases the risk of disease relapse. However, studies have not shown an increased incidence of leukemia relapse in children who receive varicella vaccine while on treatment [10–12].

A retrospective study from the Children's Oncology Group on 472 Children with ALL on maintenance chemotherapy who were unimmunised against varicella reported the 120 varicella exposure was documented in 75 children [13]. Ninety percent of the exposed children received varicella intravenous immunoglobulin (IVIG) and scheduled chemotherapy was interrupted by 1–6 weeks in exposed children. Twenty-nine of the exposed children developed varicella despite receiving IVIG and an additional 31 children without a history of exposure to varicella also developed varicella. The total cost of treating varicella in this cohort of patients in the 1980s was half a million US dollars and the authors estimated that a vaccination strategy to prevent varicella infection in the patients would have cost only 81000 US dollars. Patients who developed varicella had further prolonged interruption of chemotherapy. The authors concluded that patients with ALL who develop varicella infection

have more morbidity, prolonged hospitalization, and interruption of maintenance chemotherapy than children who develop vaccine-induced varicella. The varicella vaccine also protects against debilitating varicella zoster in the future. The incidence of varicella zoster is lesser in patients with ALL who receive the vaccine compared to those who have a natural infection [14].

Recommendations are not to give chemotherapy or intrathecal methotrexate concurrently with varicella vaccine due to the increased risk of hepatitis and transverse myelitis respectively [15]. However, studies have shown that it is safe to give varicella vaccine without interruption of oral maintenance chemotherapy [16–18]. Forty-one percent of patients in our study developed vaccine-induced varicella and these patients required interruption of maintenance chemotherapy. We also observed like other investigators that the rash associated with vaccine-associated varicella was maculopapular in contrast to the classical vesicular eruption's characteristic of varicella. All our patients with vaccine-induced varicella received acyclovir. It has been observed that acyclovir does not hinder the development of immunity to the vaccine strain [19].

Published literature over the last 4 decades that includes multicentre prospective trials in patients with ALL who were immunised with varicella vaccine has shown that the varicella vaccine is safe and efficacious and the benefits of varicella vaccine far outweigh the risk of complications of the vaccination [7–20]. The National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Varicella Vaccine Study in the United States included 548 children with ALL in remission immunised with varicella vaccine between 1980 and 1990 [14]. The study reported a 13% incidence of breakthrough varicella in those who received the vaccine. All the children with breakthrough varicella had a mild infection and there was no vaccine-related complications. Fifty percent of the vaccinees developed a vaccine-induced rash which is comparable to our findings. The seroconversion rate in this study after one dose of vaccine was 85% and after two doses it increased to 90%. The immunity in vaccinated children persisted for a long time with more than 90% vaccinees show protective antibodies a decade later. A recent study from the Netherlands reported the immunisation of 31 children with cancer among whom 23 were receiving chemotherapy for acute leukemia against varicella [16]. They reported a seroconversion rate of 70% with a single dose of the vaccine. Seven patients developed a fever with a rash. None of the patients required interruption of chemotherapy. Another study from the Netherlands reported on the outcomes of 45 children with ALL receiving maintenance chemotherapy who were vaccinated against varicella [17]. Nine out of 45 patients developed varicella despite vaccination. The presence of vaccine-associated rash was associated with a reduced risk of developing late-onset varicella. Thirty-three percent of patients had disruption of their maintenance chemotherapy due to vaccine-induced rash. The Varicella Vaccine Collaborative Study evaluated the effectiveness of the varicella vaccine in 575 children with ALL in remission treated in the USA and Canada [12]. Chemotherapy was stopped 1 week before and after the vaccination in most children. The study concluded that the varicella vaccine was safe, effective and immunogenic in leukemic children at risk of severe complications and death from varicella infection. Rash was observed in 50% of the patients one month after immunisation and was mild. There was no serious vaccine-associated adverse effect reported. The breakthrough varicella rate in patients exposed to household contacts was 14%.

Although there are numerous studies on the safety and efficacy of the varicella vaccine in children with leukemia there has been only been one death reported due to disseminated varicella infection post varicella vaccination [21]. This single report should not dissuade against the use of the varicella vaccine in children with ALL when countless more lives can be saved in LMIC with the vaccine.

Varicella vaccination is not recommended during the induction and consolidation phase of ALL treatment and therefore, the vaccination strategy of giving the vaccine at the start of the maintenance does not directly protect the children undergoing induction or consolidation chemotherapy, however, it protects indirectly by increasing the herd immunity of patients undergoing treatment and thereby reducing varicella outbreaks in the hospital.

The possibility of transmission of vaccine-induced varicella is rare [22,23]. There are reports of transmission of the varicella vaccine virus from individuals with a vaccine-induced rash to unimmunised persons. However, the transmitted vaccine virus has been found to be attenuated and the resulting contact illness mild [24,25]. It is recommended that unimmunised parents and siblings of patients with acute leukemia are immunised against varicella to protect the patient against transmission of varicella from close contacts [26,27]. Majority of children in our study who developed vaccine-induced varicella were managed on an outpatient basis and did not require isolation as their symptoms were mild. There was no documented transmission of the varicella vaccine virus in our study.

The major limitations of the study include its retrospective nature and therefore, the possibility of inadequate capture of vaccine-induced complications and reactions, non-measurement of varicella antibody levels pre and post vaccination and we did not capture the incidence of varicella infection in non-immunised patients.

In summary, in countries without universal varicella vaccination and high incidence of varicella, a single dose of varicella vaccine given to children with ALL during the start of maintenance chemotherapy is safe and effective in preventing varicella. In LMIC a vaccination strategy against varicella in patients with ALL prior to starting maintenance can be cost-effective and reduce the burden of varicella infection.

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