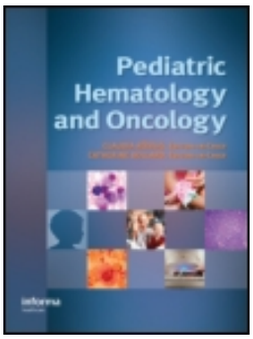

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Seroconversion Status After Single Dose and Double Doses of Varicella Vaccination in Children With Leukemia

F. Betul Cakir,[1] Cetin Timur,[2] Asim Yoruk,[2] Erkan Cakir,[3] and Aylin Canbolat Ayhan[2]

[1]Department of Pediatric Hematology-Oncology, School of Medicine, Bezmialem Vakif University, Istanbul, Turkey; [2]Clinics of Pediatric Hematology-Oncology, Goztepe Government Education and Research Hospital, Istanbul, Turkey; [3]Division of Pediatrics, School of Medicine, Bezmialem Vakif University, Istanbul, Turkey

Although varicella is a benign self-limiting disease in healthy children, it can be fatal when it occurs in immunocompromised hosts. Despite that immunosuppressed children are suggested to require 2 doses of vaccine to achieve seroconversion, conflicting results are reported in the literature. The aim of this study was to investigate the seroconversion status and mean antibody titers at first year after single dose and double doses of varicella vaccination in acute lymphoblastic leukemia patients. Patients with leukemia in remission for at least 1 year who were seronegative for varicella-zoster virus immunoglobulin G (IgG) were vaccinated. Titers above the cutoff level (0.65) were accepted as seroconversion. Seventeen patients were vaccinated with single dose whereas 24 patients were vaccinated with double doses. Mean prevaccination antibody titers were 0.56 ± 0.05 in patients with single dose and 0.51 ± 0.08 in patients with double doses ($P > .05$, Student t test). The mean antibody titers at first year were 0.61 ± 0.05 in patients with single-dose vaccination ($P > .05$, Wilcoxon signed-rank test) and 1.48 ± 0.04 in patients with double doses ($P < .001$, Wilcoxon signed-rank test). Seroconversion after single-dose vaccination was achieved in 29% of patients ($n = 5/17$) and in 75% of patients with double doses ($n = 18/24$) at first year ($P = .004$, chi-square test). These results suggest that seroconversion after single-dose vaccination might not persist at first year in malignancy patients. Double doses should be applied in order to provide long-term seroconversion.

Keywords leukemia, pediatric, vaccination, varicella

INTRODUCTION

Varicella is one of the most frequent contagious diseases of childhood [1]. Although varicella tends to be a mild disease in healthy children, the mortality and the risk of serious complications are greatly increased in immunocompromised hosts. Besides, exposure to varicella often results in delay of scheduled chemotherapy in children with malignancy, increasing the risk of progression of underlying disease [2]. Thus varicella vaccination is vital in patients with malignancy. Despite that immunosuppressed children are suggested to require 2 doses of vaccine to achieve seroconversion, conflicting results are reported in the literature [3–8]. In this study, we aimed to investigate the

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Address correspondence to Fatma Betul Cakir, Department of Pediatric Hematology-Oncology, School of Medicine, Bezmialem Vakif University, Vatan Street, Fatih 34093, Istanbul, Turkey.
E-mail: fbetulcakir@gmail.com

seroconversion status and mean antibody titers after single dose and double doses of varicella vaccination at first year in acute lymphoblastic leukemia (ALL) patients.

MATERIALS AND METHODS

Study design and patients

ALL patients, categorized as standard and moderate-risk patients according to Berlin-Frankfurt-Münster (BFM) 2000 protocol, in remission for at least 1 year with no chickenpox history were enrolled to the study. They were screened for varicella-zoster virus (VZV) immunoglobulin G (IgG) serology. Serum samples were tested for antibodies against VZV by enzyme-linked immunosorbent assay (ELISA) as already described in the literature [9]. The optical density at 405 nm was read with an ELISA microplate reader. Titers above the cutoff level (0.65) were accepted as seroconversion. Seronegative ALL patients were vaccinated. VZV IgG titers were measured 6 weeks later and patients who are still seronegative were revaccinated. We looked for all antibody titers after 1 year of the first vaccination to both singly and doubly vaccinated ALL patients. Maintenance chemotherapy was suspended 1 week before and after immunization. All the children were immunized with the same lyophilized lot of live-attenuated Oka strain varicella vaccine Biken, produced by Biken Institute, Osaka, Japan (Varilrix; SmithKline Beecham). The contents of each vaccine vial was freshly reconstituted with 0.5 mL of sterile water just before use and injected subcutaneously in the right or left deltoid area. One dose (0.5 mL) of vaccine contained no fewer than 1000 plaque-forming units. The study was approved by the local ethics committee. Informed consent was obtained from the parents after explanation the study. The parents were asked to report fever, rash, or any unexpected symptoms after each injection of vaccine and to bring the patient for follow-up to the hospital. Side effects were monitored daily by parents for 2 months after vaccination.

Statistical analysis

SPSS 11.0 program was used for statistical analysis. Two independant groups were compared with Pearson chi-square test for cathegoric variables. Student t test was used for comparisons of continuous variables between 2 independant groups. Dependant groups were compared with Wilcoxon SIgned-rank test for continuous variables. Significance level was accepted with $P < .05$.

RESULTS

Sixty-one ALL patients in remission for at least 1 year with no chickenpox history were enrolled to the study. Twenty children who were found to be seropositive for VZV were excluded. Thus, 41 seronegative ALL patients from 61 ALL children were enrolled to the study. There were 19 girls and 22 boys with ages ranging from 5 years to 15 years (median 9 years). We checked for lymphocyte levels in all ALL patients. The range was 1500–1900/mm^3 (mean 1658 ± 128). Twenty-four patients who were found to be seronegative after 6 weeks of vaccination were revaccinated. Mean prevaccination antibody titers were 0.56 ± 0.05 in patients with single dose and 0.51 ± 0.08 in patients with double doses ($P > .05$, Student t test). The mean antibody titers at first year were 0.61 ± 0.05 in patients with single-dose vaccination ($P > .05$, Wilcoxon signed-rank test), and 1.48 ± 0.04 in patients with double doses ($P < .001$, Wilcoxon signed-rank test) (Table 1). Seroconversion after single-dose vaccination was achieved in 29% of patients ($n = 5/17$) and in 75% of patients with double doses ($n = 18/24$) at first year ($P = .004$, Chi square test) (Table 2). Maculopapular or papulovesicular rashes occurred after the first dose, between 15 and 31 days, in 3 patients whose maintenance

TABLE 1 Outcome of Mean Antibody Values After 1 Year of Single and Double Doses of Vaccination

		Mean antibody value (mean ± SD)	P^*
Single dose–vacinated patients ($n = 17$)	Prevaccination	0.56 ± 0.05	$>.05$
	Postvaccination	0.61 ± 0.05	
Double dose–vaccinated patients ($n = 24$)	Prevaccination	0.51 ± 0.08	$<.001$
	Postvaccination	1.48 ± 0.04	

*Wilcoxon signed-rank test.

chemotherapies were interrupted. They were treated with acyclovir successfully. No rash occured after second doses. No local reaction was observed at the injection site.

DISCUSSION

In this study we established that double doses of vaccination was significantly more effective than single dose at first year in terms of both seroconversion rate and mean antibody titers in ALL children. Seroconversion rates after single-dose vaccination varied greatly (from 19% to 96%) in immunocompromised patients [3, 10]. Despite that waning immunity was demonstrated over time after single dose of vaccination, conflicting results are reported in the literature [3–8]. Gershon and Steinberg [8] revealed, in their multicenter study, that 2 doses of vaccine appeared to be no more effective than a single dose during follow-up years. Additionally, Gershon and Steinberg [11] suggested that there is no clear advantage to administering a routine booster dose of vaccine to vaccinees who have undergone seroconversion after one immunizing dose. On the contrary, there are smaller studies suggesting that 2-dose regimens are necessary for immunocompromised children [4–7]. Although Austgulen [4] established 85% seroconversion in 20 solid tumor patients after 4 weeks of vaccination, and reported no detectable antibodies at first year against VZV. Austgulen suggested revaccination probably within 6 months after first vaccination. Ninane et al. [5], in their study including 31 children with acute leukemia and solid tumor, revealed 70%, 85%, 75%, and 40% varicella serum antibodies at 1, 2, 3, and 12 months after vaccination, respectively. Thus, in immunocompromised patients, they recommended booster doses of the vaccine at relatively short intervals. Likewise in our study, whereas seroconversion rate was found to be 75% with double doses of vaccination, it decreased to 29% with single dose of vaccination at first year. Accordingly, although prevaccination antibody titers did not change after single-dose vaccination at first year, they significantly increased with double doses of vaccination.

Varicella vaccination is still investigational in the United States in immunocompromised patients such as ALL patients. Vaccination should be considered in ALL patients after remission for a year, otherwise at 3 to 6 months post completion of therapy. Local irritation at the injection site, fever, and rash are the most frequent adverse effects of varicella vaccination [12]. Similarly, maculopapular and papulovesicular rashes

TABLE 2 Outcome of Seroconversion Status After 1 Year of Varicella Vaccination

Vaccination status	Seroconversion n (%)	P^*
Single dose ($n = 17$)	5 (29.4)	.004
Double dose ($n = 24$)	18 (75)	

*Chi-square test.

occurred after the first dose in our 3 patients. No local reaction was observed at the injection site.

In conclusion, seroconversion after single-dose vaccination might not persist at first year in malignancy patients. Double doses should be applied in order to provide long-term seroconversion.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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