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Varicella vaccination in pediatric oncology patients without interruption of chemotherapy

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ABSTRACT

Background: Morbidity and mortality from primary varicella-zoster virus (VZV) infection is increased in immunocompromised children. Vaccination of VZV-seronegative cancer patients with live-attenuated varicella vaccine is safe when chemotherapy is interrupted. However, VZV vaccination without interruption of chemotherapy would be preferable.
Objective: To vaccinate VZV-seronegative pediatric oncology patients with live-attenuated VZV vaccine without interrupting their chemotherapy.
Study-design: We performed a single-center prospective cohort study.
Results: Thirty-one patients with either a hematological malignancy ($n = 24$) or a solid tumor ($n = 7$) were vaccinated early during their course of chemotherapy. VZV IgG seroconversion occurred in 14 of the 31 patients (45%) after one vaccination. Only 20 patients were revaccinated after 3 months. These were patients who did not seroconvert (5 patients) and patients who serocoverted (15 patients) to induce or sustain seropositivity. Of these 20 patients the final seroconversion rate was 70%. Seven out of the 31 patients (23%) developed a mild rash of which 5 were treated with antivirals and recovered completely without interrupting chemotherapy, and 2 recovered untreated. Of these 31 immunized patients 26 were available for cellular testing. After one vaccination 20 of 26 patients (77%) tested positive for VZV-specific $CD4^+$ T cells, of which 7 patients had remained VZV-seronegative. After the second vaccination 11 of 11 patients showed VZV-specific $CD4^+$ T cells to sustain positivity, although 4 remained VZV-seronegative.
Conclusions: This study indicates that live-attenuated VZV vaccine can be safely administered to closely monitored pediatric oncology patients without interruption of chemotherapy and adaptive immunity was induced despite incomplete seroconversion.

1. Background

Varicella (chickenpox) is a highly infectious, usually self-limited disease caused by the varicella-zoster virus (VZV). In the past the complication-rate of chickenpox in children with a malignancy was approximately 30% [1–3]. With antiviral therapy the outcome improved, the overall mortality currently is 0.05–1% [4–7]. 25% of pediatric oncology patients encounter chickenpox during treatment and 16-20% of these patients will experience morbidity due to complications of this infection [4,8]. Approval of live-attenuated varicella vaccine in the USA was in 1995 for routine use in healthy persons older than one year of age who are susceptible to VZV. Other countries followed shortly and Japan, Korea and most states of the USA have included varicella vaccination in their national vaccination schedule. The vaccine induces long-term humoral and cellular immunity in children and adults [9,10]. Since the implementation of VZV vaccination, a marked decline in the number of cases of varicella and a trend towards less hospitalizations due to chickenpox has been observed [11].

However not all children are vaccinated. It would be of great benefit to vaccinate VZV-seronegative oncology patients. We know

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that vaccination of leukemia patients in remission is feasible [12]. Although cell-mediated immunity is elicited less reliably in leukemic children after varicella vaccination than in healthy children, it appeared that the administration of VZV vaccine under controlled conditions can be beneficial to leukemic patients [12,13]. One would prefer to vaccinate in the early phase of treatment, as reported in a small pilot study achieving a seroconversion rate of 77% [13]. Mild side-effects were observed in 12.5% of the patients consisting of a varicelliform rash and fever. However, in this study chemotherapeutic treatment was delayed in order to vaccinate the children. Vaccination of patients with lymphocytes >700/mm^3, without stopping chemotherapy and without interruption of steroids 14 days before vaccination until one week after vaccination, led to an unacceptably high incidence of complications and severe rashes [14–16], and one fatal case [17]. Prevention of chickenpox during treatment for a malignant disorder remains an important goal, while considering feasibility and safety as the major guiding principles.

1.1. Objective

To investigate the safety and efficacy of VZV vaccination of VZV-seronegative pediatric oncology patients, without interruption of chemotherapy, and respecting the rule not to vaccinate during the phase in which steroids are given, or when a low number of circulating lymphocytes is present.

1.2. Study design

1.2.1. Patient selection

Newly diagnosed pediatric oncology patients who tested negative for VZV IgG antibodies and were never vaccinated before against VZV, were included in this single-center study at the Academic Medical Centre in Amsterdam, The Netherlands. Eligibility criteria included hematological and solid tumor patients on chemotherapy, who had circulating lymphocyte counts of >700/mm^3, without bulky disease and without septicemia at the time of vaccination. All children were treated according to European protocols included in the DCOG (Dutch Cancer Oncology Group) database. VZV vaccination was administered in a steroid-free phase of the treatment regimens one week before and one week after vaccination. The study was approved by the local medical ethical committee. Written informed consents were obtained from the parents of the patients and from the patient if 12 years of age or older.

1.2.2. Vaccination protocol

Varicella vaccine (Varilrix, GlaxoSmithKline UK, Uxbridge, UK; containing the attenuated VZV Oka-strain) was administered subcutaneously to eligible patients (day 0). A second dose of the vaccine was given at 3 months after the first dose. Clinical parameters were registered on the base of questionnaires and physical examination on day 0, 7, 14, 21, 28 and 3 months after vaccination. Parameters recorded by the questionnaires included: fever (>39 °C), headache, vomiting, diarrhea (defined as >6 loose stools a day), coughing, and pain, rash or induration at the injection-site. Parameters recorded on physical examination included: temperature, organomegaly (upon vaccination), skin lesions, and signs of infection. Standard laboratory tests were performed, including a complete blood cell count (CBC), creatinine, and liver enzymes. To determine the immunological response to vaccination, peripheral blood samples were drawn from the patients at each visit. Peripheral blood mononuclear cells (PBMCs) were isolated from blood and cryopreserved until analysis. To monitor infectivity of the vaccinated patients, throat-swabs were taken twice a week, for 6 weeks following the first vaccination.

1.2.3. Laboratory parameters for VZV infection

VZV specific IgG seroreactivity was determined qualitatively using a varicella-zoster IgG assay, following the instructions of the manufacturer. (miniVidas, Biomerieux, Marcy l'Etoile, France. VZV IgG was positive for sample-to-standard-ratios ≥0.90; equivocal between 0.60 and 0.90; and negative when <0.60). The equivocal results will be regarded as positive Quantitative PCR (qPCR) for the viral load was performed in blood samples and in throat swabs as described before [18].

1.2.4. Immunofluorescent staining and flow cytometry

PBMCs were used to determine the absolute numbers and percentages of CD4$^+$ and CD8$^+$ T cells, B cells and NK cells (MultiTest IMK kit, BectonDickinson [BD] Biosciences, Franklin Lakes, NJ, USA). Using 20 μl of the multiset antibody mix, either CD3/CD8/CD45/CD4 or CD3/CD16CD56/CD45/CD19 was added to 50 μl blood in two different TruCount tubes (BD). Cell viability was determined after freeze-thawing and the absolute numbers and percentages of lymphocyte cell populations were determined by the Multiset program (BD) on a FACSCalibur (BD), 6×10^5 T cells per stimulus were used. Controls were included in each experiment.

1.2.5. Determination of VZV-specific T cells by proliferation

For antigen-specific T-cell activation VZV-antigen was used in a final concentration of 20 μl/ml, previously defined as the optimal dose for stimulation of PBMCs [19]. For proliferation, PBMCs at 5–10 × 106 cells/ml were labeled with 0.5 μM (final concentration) of 5,6-carboxyfluorescein diacetate succinimidyl ester (CFSE; Molecular Probes, Paisley, UK), washed and resuspended in culture medium for six days. T cells were stimulated with VZV-antigen, combination of αCD3/αCD28 MoAbs at saturating concentrations as described before [20].

1.2.6. Statistics

SPSS 20.0 was used as data base and analysis tool. Where applicable, differences between means were tested by Student *t*-test. Because of the small sample size most data were described descriptively.

2. Results

2.1. Patient characteristics

Thirty one VZV-seronegative pediatric oncology patients were included in this study from February 2002 until May 2010 with for each patient a minimum of 5 years of follow-up for the children who survived. All children were treated according to DCOG (Dutch Cancer Oncology group) included protocols. Patient characteristics are presented in Table 1. Chemotherapy was not stopped or delayed because of VZV vaccination.

2.2. Laboratory results

White cell counts and liver enzymes of the patients are summarized in Table 2. The hematology patients had higher liver enzymes as compared to the patients with solid tumors, although the difference did not reach significance. The hematology patients received high doses of methotrexate, which can explain the elevated liver enzymes. The liver enzymes normalized in all patients within three months after vaccination. No significant differences in the numbers of CBCs, lymphocytes or neutrophils were detected comparing patients with a hematological malignancy or a solid tumor (Table 2).

Table 1
Patient characteristics.

Patients (*N*) = 31	Hematology	24	
	Solid	7	
Age (years)	Hematology	4.1 (2.9–16.9)	*P* = 0.57 (NS)
(At time of vaccination)	Solid	2.9 (1.8–5.3)	
Time (weeks)			
Start chemotherapy to first vaccination (mean)	Hematology	14.2 (6–36)	*P* = 0.75 (NS)
	Solid	18.5 (8–36)	
Adverse effects			
Skin lesions (number of patients)	Hematology	5 (21%)	*P* = 0.67 (NS)
	Solid	2 (28%)	
Treatment with antivirals (number of patients)			
	Hematology	4 (16.6%)	*P* = 0.88 (NS)
	Solid	1 (14.2%)	
Seroconversion			
1st vaccination (*n* = 31)	Hematology (24)	10 (41.5%)	Total 14 (45%)
	Solid (7)	4 (57.2)%	
2nd vaccination (*n* = 20)	Hematology (15)	10 (67%)	Total 14 (70%)
	Solid (5)	4 (80%)	

Table 2
Laboratory results as mean (range) on day 1 of first vaccination.

	Hematology *N* = 24	Solid *N* = 7	*P* value
Neutrophils (x10^6/l)	2382 (770–4650)	2576 (240–6000)	*P* = 0.71 (NS)
Lymphocytes (x10^6/l)	2190 (700–6830)	1151 (400–2700)	*P* = 0.11 (NS)
White cell count (x10^9/l)	5.4 (1.8–10.2)	5.1 (3.8–7.8)	*P* = 0.76 (NS)
ALAT (IU)	106 (14–820)	41.8 (20–88)	*P* = 0.39 (NS)
ASAT (IU)	118 (14–519)	43.3 (22–62)	*P* = 0.24 (NS)

Table 3
VZV-specific CD4$^+$ T-cell activity after the first and second vaccination.

Vaccination 1 (*n* = 26)	Seronegative	Seropositive	
T-cell positive	7	13	20
T-cell negative	5	1	6
Total	12	14	26
Vaccination 2 (*n* = 11)	**Seronegative**	**seropositive**	
T-cell positive	4	7	11
T-cell negative	0	0	0
Total	4	7	11

2.3. Adverse effects and virology

To determine whether the patients were contagious after vaccination, VZV was monitored for 6 weeks following the first vaccination. VZV-DNA was detected by PCR in all 4 throat swabs of these patients, while viral cultures taken in parallel all remained negative.

In 6 of the 31 vaccinated patients VZV DNA became detectable in peripheral blood within 6 weeks after vaccination (median peak value 7500 VZV DNA copies/ml, range 40–10,000 copies/ml). No household exposure to chickenpox was documented during this period. Five of these 6 viremic patients seroconverted in response to the first vaccination.

In 7 patients (22.5%) mild adverse effects were observed within 10 days after vaccination. They developed a rash (<50 vesicles). According to the clinical score of Vazquez et al. [21], all 7 patients were considered to have mild disease. Four of these 7 patients were treated with oral valacyclovir (total of 7 days); 1 with intravenous acyclovir because of mucositis (total of 7 days) which precluded oral medication; and 2 patients did not receive antiviral treatment. All 7 patients with adverse effects after vaccination recovered without interruption of chemotherapy.

2.4. Immunogenicity of the vaccination

VZV-specific IgG could be detected in 14 of the 31 patients (45%) after the first vaccination. The majority of these patients (80%) seroconverted within 6 weeks after VZV vaccination. Seroconversion did not correlate with the age at vaccination ($p = 0.35$), the time between start of chemotherapy and vaccination ($p = 0.49$), or with the number of circulating lymphocytes at the time of vaccination ($p = 0.19$). Twenty patients received a second dose of vaccine. The remaining 11 patients were not vaccinated a second time because of various reasons, ranging from no consent from the parents for the second vaccination, to patient related reasons, such as a relapse of the primary disease, making re-vaccination too risky. After the second dose of vaccine in 20 patients (3 months after the initial dose), the IgG seroconversion rate increased to 70% (Fig. 1). Of these 14 patients 4 converted from IgG-seronegative to seropositive, 5 converted from borderline seropositivity to seropositive, and remaining patients were already IgG-seropositive after the first vaccination and consented to receive a second vaccination to further sustain positivity.

During the first year after chemotherapy, environmental or household contacts to wild-type VZV were documented in 5 patients (16%). The first patient (1 vaccination IgG seronegative but positive VZV-specific CD4$^+$ T-cell activity) showed no clinical signs of varicella upon contact and was therefore not treated. The 4 other patients all vaccinated twice all seronegative after first vaccination, 2 seropositive after 2 vaccinations and all showed positive VZV-specific CD4$^+$ T-cell activity (all hematological patients) developed a varicelliform rash (50–200 lesions) and reported their varicella contact within 3 days after chickenpox exposure (6–12 months after VZV vaccination) were treated as soon as vesicles appeared. Two had a Vazquez-score of 13 and appeared moderately ill (the seronegative patients after 2 vaccinations). Both recovered rapidly after start of acyclovir intravenously, having in retrospect a relatively normal viral load (wild-type VZV-DNA loads peaking at 12,000 and 42,500 copies/ml) [18]. The 2 other patients (seropositive patients after 2 vaccinations) had a Vasquez-score <7 and were treated with oral valacyclovir. All these patients showed a mitigated clinical course as compared to an IgG-negative immunocompromised patient with wild-type VZV infection in another study, who had not been vaccinated and showed a viral load up to 1,000,000 copies/ml [22].

2.5. Occurrence of VZV-specific CD4$^+$ T cells

A VZV-specific CD4$^+$ T-cell proliferation assay could be performed in 26 patients after the first vaccination, of which 13 patients showed seroconversion and T cell positivity (Table 3, Fig. 1). Twenty of these 26 patients showed VZV-specific CD4$^+$ T-cell reactivity (of which 7 were VZV-IgG negative) (Fig. 2A and

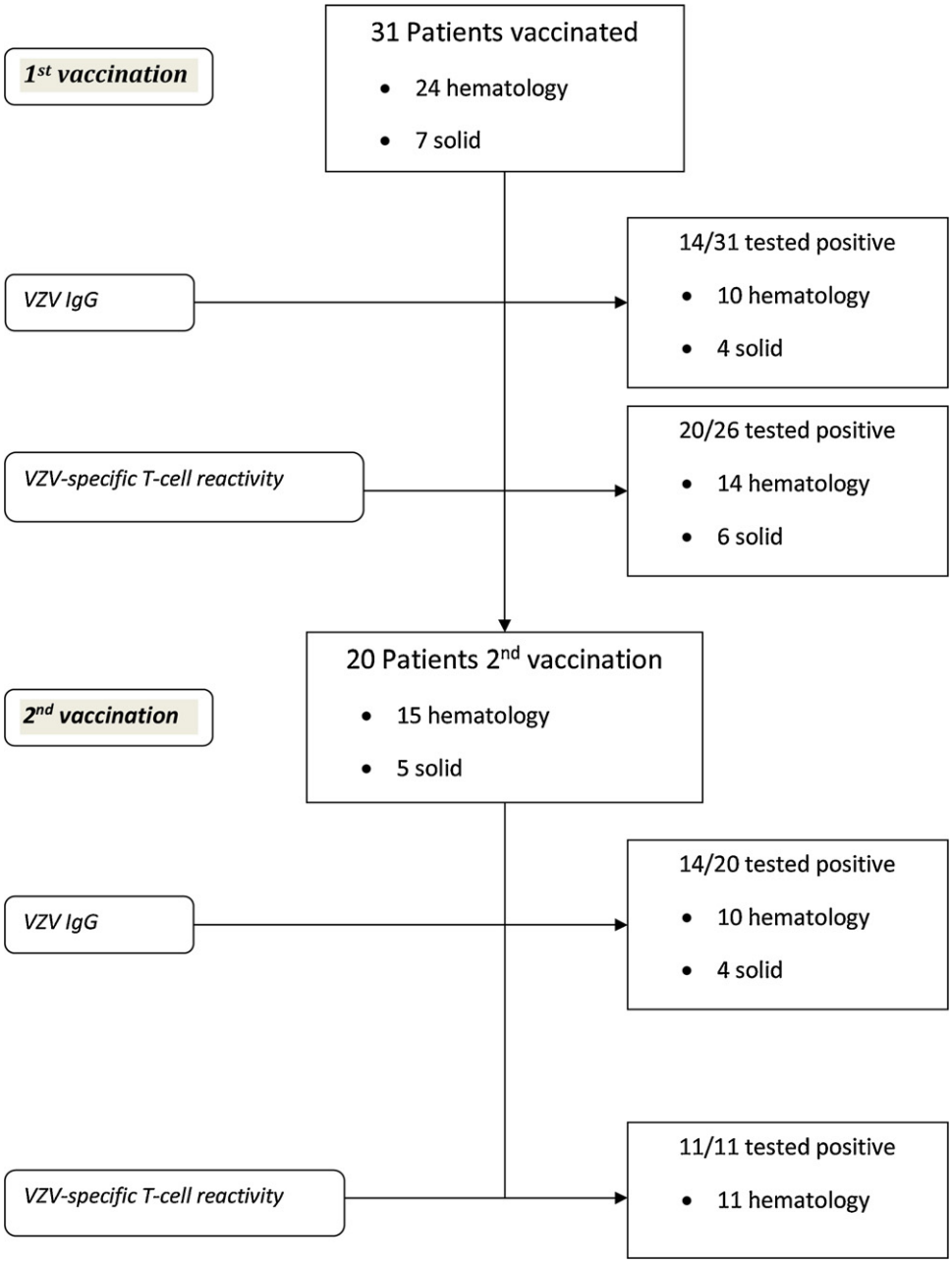

Fig. 1. Flow diagram of the VZV vaccination study.
The diagram shows the number of patients with one or two vaccinations and the number of patients of whom VZV T-cell reactivity has been tested in the available blood samples.

Supplementary Figure). After a second vaccination the assay could be performed in 11 patients, all 11 patients (4 remained IgG-seronegative) showed VZV-specific T-cell proliferation (Table 3, Fig. 2A). The assay could not be completed in all patients because of lack of blood samples; examples of kinetics in VZV-specific T-cell responses over time have been added for reasons of clarity (Fig. 2B).

3. Discussion

This is the first report of a cohort of pediatric oncology patients who received live-attenuated VZV vaccine in a relatively early stage of treatment without interrupting chemotherapy. The criteria that no steroids are given one week before and one week after vaccination, lymphocyte counts should be >700/mm^3, and that the child has no bulky disease, were all met. Adverse effects of vaccination in our cohort were limited to a mild rash observed in 7 patients (22.5%), accompanied by fever in 3 patients (9.6%). The occurrence of adverse effects in these patients did not correlate with the number of circulating lymphocytes on the first day of vaccination. All patients recovered without interrupting chemotherapy. We are aware of the possible bias that we were extremely cautious looking for these side effects possibly treating them very early. Although seroconversion rates after a single dose of vaccine were lower in our cohort compared to the LaRussa cohort (45% vs. 82%) [12], the data from the present study are encouraging since severe disease in this susceptible population did not occur following vaccination during or after chemotherapy.

Upon infection, VZV is believed to be contained by the concerted action of antibodies, T cells and NK cells [23–25]. It was encouraging to find that out of 26 patients tested for VZV-specific T-cell activ-

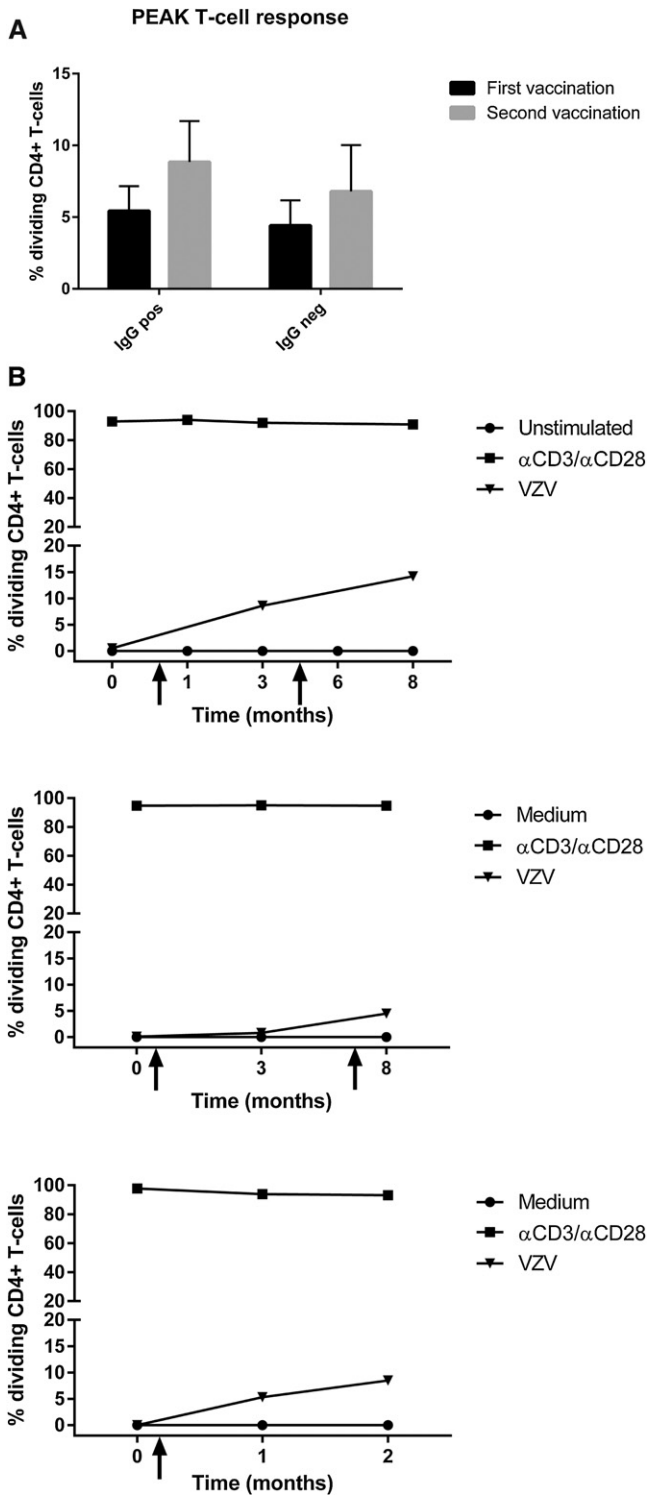

Fig. 2. VZV-specific T-cell reactivity.
A: Bargraph representing VZV-specific CD4 $^{+}$ T-cell proliferation in IgG-positive and IgG-negative patients as shown for primary and secondary VZV immunizations.
B: Time curves in three patients with different patterns of humoral and T-cell reactivity. The upper panel illustrates a case with a steady rise in positive IgG titer at 3 and 6 months. The middle panel represents a case with marginal IgG response at 3 months, IgG-negative at 6 months following vaccinations—being IgG-positive at 1 year of follow-up in the absence of documented chickenpox contact or overt clinical breakthrough infection. The lower panel represents a case with negative IgG at 3 months and positive IgG titer at 6 months post-vaccination.

ity 77% were found positive after the first immunization and that of these 66% showed seroconversion. After a second vaccination 100% of the patients tested showed VZV-specific T-cell activity at a similar seroconversion rate. In 5 patients who developed wild-type varicella during follow-up the varicella vaccination seemed to protect from the development of severe disease, however it is likely that the vaccinees reported exposure and disease sooner than most other immune compromised children would have, since they were informed about this as part of the study, and were probably treated sooner.

But in our experience, as well as previously described in literature [26,27], unvaccinated cancer patients develop severe chickenpox upon exposure. In the patients with exposure to chickenpox who developed a mitigated course of varicella, we noticed that virus-specific T cells were clearly induced within 14 days after appearance of the rash (own patients). These data suggest a suboptimal induction of adaptive immunity upon immunization, rather than primary vaccine failure. VZV-specific CD4^{+} T cells were induced upon vaccination, after 2 vaccinations even in 100% of the analyzed patients (total of 11 patients). In this respect, it is known that VZV-specific CD4^{+} T cells can be detected in healthy children upon vaccination and also show the response that they develop less severe varicella on exposure [28]. Leukemic patients develop less pronounced VZV-specific T-cell responses upon chickenpox infection [25]. Therefore, the frequencies of these cells are higher in healthy children than in our patients, which are detected by their antigen-specific proliferative T-cell responses.

Potential transmission of the attenuated VZV strain to other immunocompromised children was stringently monitored yet not encountered. Although VZV-DNA was detected by PCR at borderline levels in 4 throat swabs from 4 patients upon weekly monitoring, the viral cultures from the oropharynx taken in parallel all remained negative. This finding is in accordance with the findings in oropharyngeal secretions from vaccinated controls [29]. However, the vaccinated patients that develop cutaneous vesicular lesions are infectious from these lesions as proven by viral culture of vesicle fluids or scrapings. In this group of patients precautions for isolation need to be taken,such as protective isolation although the virus will still be live-attenuated to its close contacts [29].

For unvaccinated and vulnerable patients such as pediatric oncology patients, a well-targeted VZV vaccination strategy, such as the one applied in this study, seems promising under close monitoring. After VZV vaccination, the clinician may decide to withhold preventive measures such as the intramuscular administration of VZV-specific antibodies upon VZV contact, even when the immunocompromised patient has remained seronegative after 2 vaccinations. The patient's T-cell reactivity is likely to prevent severe varicella, and if varicella would be clinically progressive, valacyclovir or acyclovir may be administered.

Our study demonstrates that a varicella vaccination strategy in the newly non-vaccinated IgG-negative pediatric oncology patient is possible, without interruption of chemotherapy, showing seroconversion of 70% after 2 vaccinations. This strategy offering 2 doses will need to be confirmed in a larger study. In this larger study follow up data on persistence of antibody levels to indicate how good immune memory is needs to be performed.

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Ethical approval

This study was approved by the medical ethical board of the Academic medical center Amsterdam, the Netherlands.

Conflict of interest

Dr. Huib Caron started working for F. Hoffman-La Roche Ltd., and Dr. Mireille Vossen started working for Teva Pharmachemie after the final version of this manuscript was drafted and there was no conflicting relationship with this current study. All other authors reported no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcv.2016.01.004.

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