ORIGINAL ARTICLE

Varicella vaccination in children with lymphoma and solid tumours

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Background: Varicella infection can be a severe disease, especially in immunosuppressed patients. Here, experience with live varicella vaccine to prevent varicella infection is reported in children who were undergoing treatment for lymphoma and solid tumours.

Methods: 40 children, aged between 12 months and 15 years with no clinical history of varicella, were vaccinated with live varicella vaccine. All received two doses of the vaccine subcutaneously 4 weeks apart. Serum samples were taken before the first dose and 6 weeks after the second dose of vaccine.

Results: Before vaccination, 32 patients were seronegative for varicella and eight were seropositive. Seroconversion was observed 6 weeks after the second dose in 24 of the 32 (75%) seronegative children. In 4 of 8 previously seropositive patients, antibody titres increased after immunisation. Zoster infection occurred 5 weeks after the second dose of vaccine in only one previously seronegative child. 7 children, who had responded to the vaccine, have been exposed to varicella in their families or in school without contracting clinical disease.

Conclusion: Although the small number of patients in our group prevents us from drawing definitive conclusions, the varicella vaccine seems to be well tolerated and can be administered to children with lymphoma and solid tumours undergoing treatment.

Varicella is a common and highly contagious childhood disease caused by the varicella-zoster virus. Although varicella infection usually follows a benign clinical course in healthy children, it may be quite severe in immunosuppressed patients.[1–3] These patients usually have disseminated disease with extensive skin lesions and visceral organ involvement. The use of varicella vaccine in such patients, therefore, prevents major complications and interruption of treatment for cancer. We aimed to assess the clinical safety and efficacy of the live varicella vaccine in children with lymphoma and solid tumours.

PATIENTS AND METHODS

Patient population

Forty children with lymphoma and solid tumours, who were in remission with no history of varicella, were vaccinated with a live varicella vaccine. After a detailed explanation about the nature of this study, written informed consent was obtained from all parents. The study protocol was also evaluated and supported by the institutional review board. Inclusion criteria were as follows:

1. Primary malignancy should be in remission—that is, no evidence of tumour in clinical and radiological examinations.
2. No history of chicken pox.
3. Leucocyte count should be normal.

Tables 1 and 2 present some characteristics of each group of patients with cancer.

Vaccine

The Oka-strain varicella vaccine (Varilrix SmithKline-Beecham, London, UK) was used in the study. Each patient received a 0.5 ml vaccine dose containing no fewer than 1000 plaque-forming units of varicella virus.

Vaccination schedule

All the children received two doses of vaccine subcutaneously to the right or left deltoid area 4 weeks apart. A complete blood count test was carried out in all children. Eighteen children were vaccinated after the completion of their chemotherapy. The remaining patients were vaccinated between chemotherapy courses. Chemotherapy was interrupted 1 week before and 1 week after the vaccination.

Follow-up and serological assay

Serum samples were taken before administration of the first dose and 6 weeks after the second dose of vaccine. Serum samples were kept frozen at –20°C until determination. Antibody titres to varicella zoster vaccine were measured by ELISA as already described in the literature.[4 5] The optical density at 405 nm was read with an ELISA microplate reader. All values above the cut-off level (0.657) were accepted as

Table 1 Some important characteristics of patients

	Total	Patients with lymphoma	Patients with solid tumour
Total number	40	13	27
Sex (M/F)	24/16	8/5	16/11
Age (years)	1–15	2–15	1–13
Median	4	6	4
Follow-up since immunisation			
Range (months)	6–38	18–38	6–38
Median (months)	26	30	20
Vaccination time			
Between chemotherapy courses	22	4	18
After the cessation of chemotherapy	18	9	9
Range (months)	3–14	6–14	3–12
Median (months)	6	8	4

Table 2 Tumour types and the status of chemotherapy in the study group

Tumour type	No of patients	Chemotherapy	
		On	Off
Lymphoma			
Hodgkin's	7	2	5
Non-Hodgkin's	6	2	4
Wilms's tumour	9	7	2
Germ cell tumour	5	4	1
Rhabdomyosarcoma	4	3	1
Brain tumour	3	2	1
Neuroblastoma	3	1	2
Other	3	1	2

positive. 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. The children living in the city centre were closely followed with regular examinations at the outpatient clinic, whereas those living further away were followed up by telephone calls. Side effects were monitored daily by parents for 2 months after vaccination. Parents were also instructed to report exposures to varicella or zoster infections.

Statistical methods

Yate's correction and Fisher's exact χ^2 tests were used to investigate the relationship between vaccine response and the various clinical characteristics of the patients.

RESULTS

Serological response to the vaccine

A total of 40 children with a negative varicella history were vaccinated (table 3). Positive antibody titres were present before vaccination in eight of the 40 vaccinees. Seroconversion was observed after vaccination in 24 of the 32 seronegative children. An antibody rise was noted in four of the eight seropositive patients after vaccination. No statistically significant difference was found between patients receiving and not receiving chemotherapy. Nine patients with lymphoma were vaccinated after the end of chemotherapy, whereas the remaining four patients were vaccinated in between chemotherapy courses. Antibody responses were similar between the two groups (7/9 *v* 3/4). On the other hand, in the solid tumour group, 14 of the 18 patients receiving vaccine in between chemotherapy courses responded to the vaccine, and antibody response was positive in eight of nine patients receiving vaccine after chemotherapy.

Side effects

No major side effects due to vaccination were observed. Local pain was noted in three patients. Zoster infection occurred 5 weeks after the second dose of vaccine in only one previously seronegative child. The vaccinee who developed zoster infection was a 7-year-old boy with Hodgkin's lymphoma. He was vaccinated in between the chemotherapy courses. A four positive antibody rise with the clinical findings of zoster infection occurred 5 weeks after the second dose of vaccine. We have no proof that this was owing to the vaccine virus. The child had mild lesions and was treated with acyclovir successfully.

Table 3 Seropositivity before vaccination and antibody response to vaccination

Immune status	n	No with antibody response
Seronegative	32	24/32 (75%)
Lymphoma	10	7/10 (70%)
Solid tumour	22	17/22 (77%)
Seropositive	8	4/8 (50%)
Lymphoma	3	1/3
Solid tumour	5	3/5

Varicella immunoglobulin G (IgG) titres at cut-off levels >0.657 were generally accepted as positive.

Protection

Seven children who responded to the vaccine were subsequently reported to have been exposed to varicella in their families or in school without contracting clinical disease.

DISCUSSION

Varicella infection follows a more severe and complicated course in immunosuppressed than in healthy children.[1–3] However, advances in anti-viral chemotherapy have greatly improved the outcome in these patients.

Neverthless overall mortality has been extremely high in untreated patients. Varicella vaccination in children with malignant disease was aimed at preventing infection and the disruption of chemotherapy schedules.

Until now, live varicella vaccination in healthy children, has been reported in the literature as highly immunogenic and well tolerated.[6–8] Currently, varicella vaccination is routinely recommended in all healthy children aged between 12 months and 13 years. The results of immunisation in children with malignant disease have also been reported in several studies.[9–17] Most of the studies were carried out in children with leukaemia. In all, 82% and 95% seroconversion rates were reported after one and two doses, respectively, in one of the largest studies in children with leukaemia in remission.[10] The other reported response rates range from 61% to 94% in children with leukaemias and lymphomas. However, in children with solid tumours, experience with varicella immunisation has been less reported.[18 19] Ecevit *et al*[19] previously reported a 95% seroconversion rate after a two-dose regimen in 29 children with leukaemia and various solid tumours. In our study, a seropositivity of 75% was recorded in 32 previously seronegative children. The percentage of seropositivity in our group is similar to that in some previous reports. Arbeter *et al*[20] reported that seroconversion to the varicella vaccination in patients undergoing maintenance chemotherapy did not differ from that in children with leukaemia under suspended chemotherapy.

Similarly, in our study, there was no significant difference between the seroconversion rates of the group with continued chemotherapy and the group with completed chemotherapy.

Despite lower antibody response, the varicella vaccination seemed to provide good protection against the disease in our

study. Although seven children were exposed to varicella, there was no case of clinical varicella infection.

A major concern with varicella vaccination in children with cancer is the belief that it may not stimulate sufficient antibody responses and may cause serious side effects. We propose that general cellular immune responses should be prospectively studied before vaccination in immunocompromised children. Slordahl *et al*[13] reported that determination of specific cellular immune response to varicella antigen after vaccination was an important supplement to serological tests in the assessment of vaccine response. However, immunological evaluation could not be carried out before vaccination in our group except for counting leucocytes.

We believe that children with lymphoma and solid tumours can be immunised when they are in remission. Chemotherapy should be suspended 1 week before the vaccination and reinitiated after an interval of 7 days. Rash was reported to be the most common complication (5–25%) of vaccination.[20] Interestingly, no vaccine-associated rash was observed in our group. On the other hand, the incidence of zoster in vaccinated immunosuppressed children has been reported to be 3.8%.[19] In our study, zoster infection occurred 5 weeks after the second dose of vaccine in only one case with Hodgkin's disease. The patient was successfully treated with aciclovir. It has been reported that the incidence of zoster was less frequent and clinical symptoms less severe in the vaccinated group than in the naturally infected group.

In conclusion, our study shows that varicella vaccine seems to be well tolerated and immunogenic in children with lymphoma and solid tumours. Further large-scale investigational studies are needed to determine the use of varicella vaccination in children with lymphoma and solid tumours.

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