BIKEN JOURNAL Vol. 27, 115–118, 1984

CLINICAL OBSERVATIONS ON VARICELLA-ZOSTER VACCINEES TREATED WITH IMMUNOSUPPRESSANTS FOR A MALIGNANCY

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Between 1974 and 1983, 60 persons have been immunized at Kyushu University Hospital with a live attenuated varicella-zoster virus vaccine, Oka strain. The recipients were classified into 3 groups: those with a malignancy, those with the nephrotic syndrome and those with diseases not related to immuno-hematologic dyscrasia. The only adverse clinical reactions to the vaccine were skin rash with 3–30 vesicles and a body temperature of 38 C, which were seen in 2/21 (9.5%), 4/16 (25%) and 3/23 (13%) patients in the respective groups within 5 weeks after vaccination. From 6 months to 9 years after the vaccination, exogenous varicella infection occurred in 5/21 (23.8%), 1/16 (6.25%), and 0/23 (0%) patients in the respective groups. It is concluded that for patients with malignancies, revaccination is desirable to ensure the protective effect of the vaccine.

INTRODUCTION

Chickenpox and herpes-zoster are life threatening diseases in patients in an immunosuppressed state. Before varicella virus vaccine was developed, more than 10% of all children with malignancies, particularly leukemia, and of those being treated with anticancer drugs died from infection with wild varicella. In 1974, varicella virus vaccine was developed by Dr. M. Takahashi (Takahashi et al., 1974) and the vaccine is now an accepted form of prophylactic treatment (Asano et al., 1975; 1977; Izawa et al., 1977; Ozaki et al., 1978; Ha et al., 1980; Katsushima et al., 1982). This paper reports observations on the safety and efficacy of the vaccine in various groups of patients.

MATERIALS AND METHODS

1. *Vaccine recipients*

Sixty Japanese children with no history of chickenpox who were vaccinated between 1974 and June 1983 were classified into three groups on the basis of their underlying disease. They consisted of 21 children with malignancy or hematologic dyscrasia, 16 children with the nephrotic syndrome and 23 children with a disease not related to immuno-hematologic dyscrasia (Table 1). In general, the children were vaccinated when they were exposed to the virus in the ward or at school or home.

2. *Vaccine*

A live attenuated varicella zoster virus vaccine, Oka strain, was provided by Dr. M. Takahashi. Vials containing 500 plaque forming units of lyophilized vaccine were stocked in a deep freezer at −70 C.

TABLE 1. *Numbers and underlying diseases of the vaccinees and numbers of infectee cases after vaccination*

Year	Cases	Disease							
		L	M-L	H-X	S-T	Rbl	Oth	NS	Oths
1974	3				3				
1980	9							4	5
1981	27	8	1			1		4	13
1982	10	2		1				4	3
1983	11	2			2		1	4	2
		12	1	1	5	1	1		
Total	60	21						16	23
Infected		3	1			1		1	0

L, leukemia; M-L, malignant lymphoma; H-X, histiocytosis X; S-T, solid tumor; Rbl, retinoblastoma; Oth(s), other(s); NS, nephrotic syndrome.

3. *Serologic assays*

The immune adherence hemagglutination (IAHA) and fluorescent antibody to membrane antigen (FAMA) assays were used to test the sera obtained from children before and 1 month after vaccination.

4. *Virus culture*

For isolation of the virus, the fluid contents of the vesicles and peripheral blood mononuclear cells separated by Ficoll-Conray gradient centrifugation were used as specimens. The specimens were cultured on human embryonic lung cells (Flow 2,000) and vero cells. Both these lines are maintained in this laboratory.

RESULTS

Nine of the sixty children (15%) had eruptions and slight fever after vaccination. The eruptions were typical chickenpox vesicles in 7 of 9 children, merely maculopapules in one child and purpuric in one child. The vesicles were 3 to 30 in number on the trunk during 3 to 32 days after the vaccination. Only one child with acute lymphoblastic leukemia had a temperature of 38 C for one day. All the children were well, even during the time of clinical reactions. There was no reactivity at the site of injection and there were no untoward effects (Table 2).

TABLE 2. *Clinical symptoms at vaccination*

Group	Number	Rate (%)
1. Malignancy	2/21	9.5
2. Nephrotic syndrome	4/16	25.0
3. Others	3/23	13.0

An antibody response was evident in all but three of the children, a 14-month-old girl with acute lymphoblastic leukemia under treatment with vincrystine, cyclophosphamide and cytosine arabinoside, and a 5-year-old boy and a 6-year-old girl both with the nephrotic syndrome under treatment with corticosteroid.

Six of the sixty recipients had chickenpox between 3 and 25 months after the vaccination. One of these was a child with the nephrotic syndrome who was a non-responder in the initial vaccination. The other five had malignancies, (one had retinoblastoma, one had malignant lymphoma and three had acute leukemia) and had shown seroconversion with vaccination (Table 1). The infection was from siblings in two cases, from friends in two cases and undetermined in two cases. The symptoms of natural infection in the vaccinees varied from mild to severe. The severe case was a girl with acute leukemia who was vac-

cinated at the age of 3 years 11 months and showed an antibody response from less than 2 to 8 (IAHA) at that time. She was treated for leukemia of the central nervous system with methotrexate and vincrystine alternately once a week, with methotrexate and hydrocortisone intrathecally once a week and with 6MP and prednisolone orally every day before the time of onset of chickenpox. Eleven months after the vaccination, her temperature was 40.3 C for one week and a generalized chickenpox rash appeared and lasted for 10 days. Hepatomegaly and mild elevation of serum aminotransferases occurred. The rash consisted of more than 100 vesicles of 3–6 mm in diameter scattered from her head to the soles of her feet and hands. The vesicles were discrete and not undermined or hemorrhagic. The surrounding redness was rather broader than that seen on a person without immunological disorder. The vesicles were encrusted by 10th day. No virus could be cultured from any specimen. The antibody titer was elevated to 1: 2,048 (IAHA) on the 14th day of illness. Thus, the frequency of natural infection after vaccination was significantly higher in the group with malignancies than in the group without immunohematologic dyscrasia (Table 3, 4).

TABLE 3. *Frequency of natural infection after vaccination*

Group	Number	Rate (%)
1. Malignancy	5/21	23.8[a]
2. Nephrotic syndrome	1/16	6.25
3. Others	0/23	0[a]

[a] Significant (p=0.05).

DISCUSSION

Although it is self-evident that a live virus vaccine should be given to a healthy person or a person without an immunologic abnormality, varicella-zoster virus vaccine is considered suitable for prevention of the fatal course of chickenpox in persons with malignancies. Moreover, when given in such cases, it is thought desirable to give the vaccine during a period of remission of the underlying disease to avoid side effects of the vaccine. However, we are often compelled to give to the vaccine to patients under immunosuppressive therapy when they come in contact with a patient with varicella or herpes-zoster, because we have no other effective means of treating varicella. The present data show that there is no risk from the vaccine itself when administered during an emergency to patients being treated with immunosuppressive agents since the clinical reaction to the vaccine of these patients was not significantly more severe or more frequent than

TABLE 4. *Wild varicella infection among the vaccinees*

Name	Age	Sex	Disease	Drugs before vaccination	Antibody		Time after vaccination	Severity of chickenpox
					Pre	Post		
Y. M.	5 yr 0 mo	M	NS	Pred	<2	2	5 mo	mild
T. A.	2 yr 11 mo	F	Retino	VCR, EDX	<2	16	3 mo	mild
S. M.	8 yr 2 mo	F	AL	VCR, MTX	<2	4	10 mo	moderate
S. C.	3 yr 11 mo	F	AL	VCR, MTX	<2	8	11 mo	severe
N. T.	3 yr 5 mo	M	ALL	6MP, MTX, Pred	<2	8	23 mo	moderate
H. J.	4 yr 2 mo	F	Malg Ly	6MP, MTX, Pred, VCR	<2	8	25 mo	mild

NS, nephrotic syndrome; Retino, retinoblastoma; AL, acute leukemia; ALL, acute lymphoblastic leukemia; Malg Ly, malignant lymphoma; Pred, prednisolone; VCR, vincrystine; EDX, cyclophosphamide; MTX, methotrexate.

in persons with no immunologic abnormality. These observation support use of the vaccine in an emergency for patients under therapy with immunosuppressants. However, the data indicate that seroconversion by the vaccine may be unsuccessfull in a few patients in the immunosuppressed state. It is also noteworthy that a few vaccinees with malignancies receiving consolidation therapy were not protected against exogenous varicella, even though they showed seroconversion after vaccination. However, the facts that no virus was isolated from these patients, that the antibody increased and that no IgM antibody was detected by immunofluorescence antibody assay in these patients imply a persistence of immunological memory to varicella-zoster virus in these patients. This, I believe, saved them from a fatal course on infection. These observations suggest that revaccination is desirable to give a lasting protective effect for patients with malignancies.

ACKNOWLEDGMENT

This work was partly supported by a Grant for Scientific Research from the Ministry of Health and Welfare of Japan.

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