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EVALUATION OF VARICELLA VACCINE IN CHILDHOOD LEUKEMIA. OBSERVATION OVER 6 YEARS

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Since 1977, we have used a live attenuated varicella vaccine to immunize 10 children with acute leukemia. 8 patients had no adverse clinical reaction but 2 patients developed mild fever and papulovesicular rash after vaccination. All 9 tested children became seropositive after the vaccination. Also in all 3 children who were observed for more than 4 years, persistence of neutralizing antibody was detected. Most of the recipients were prevented from developing symptoms of varicella in spite of contact exposure. Two patients developed varicella when they were in severe immunosuppressive states but their symptoms were mild. None of the children developed herpes-zoster during the 6 year follow-up period. The results suggest that the varicella vaccine is effective in children with acute leukemia, and that long-term effectiveness can be expected.

INTRODUCTION

Since 1977, we have used the varicella vaccine to immunize 10 children with acute leukemia. Also since 1977, we have been observing the long term protective efficacy and safety of the vaccine. We shall now report the results of six years study of the vaccination of 10 children with leukemia.

MATERIALS AND METHODS

1. *Study population* (Table 1)

This study includes 10 children with acute leukemia in complete remission for more than 6 months. The children were 1 to 8 years old, all of them were receiving 6-Mercaptopurine for maintenance chemotherapy, and all had a negative history for varicella and herpes-zoster.

VACCINE AND VACCINATION

The vaccine was derived from the Oka strain of varicella-zoster virus as described previously by Takahashi et al. (1975). The immunizing dose was 500 plaque-forming units of virus and some immunological studies were performed before immunization. After vaccination, all the children were observed twice a month at the outpatient clinic of

TABLE 1. *Follow-up of recipients of vaccine*

Case No.	Age (yr)	Sex	Type	Maintenance	Clinical reaction
1	6	M	ALL	6MP, MTX	(−)
2	4	F	ALL	6MP	(−)
3	2	M	ALL	6MP	(−)
4	3	M	ALL	6MP	(−)
5	2	M	AML	6MP	(−)
6	4	M	ALL	6MP, MTX	(−)
7	1	M	AML	6MP	(−)
8	2	M	ALL	6MP, MTX	(−)
9	8	M	TALL	6MP, MTX	Rash, Fever
10	3	F	ALL	6MP. MTX	Rash, Fever

ALL=Acute lymphocytic leukemia.
AML=Acute myelocytic leukemia.
TALL=T cell acute lymphocytic leukemia.
6MP=6-Mercaptopurine.
MTX=Methotrexate.

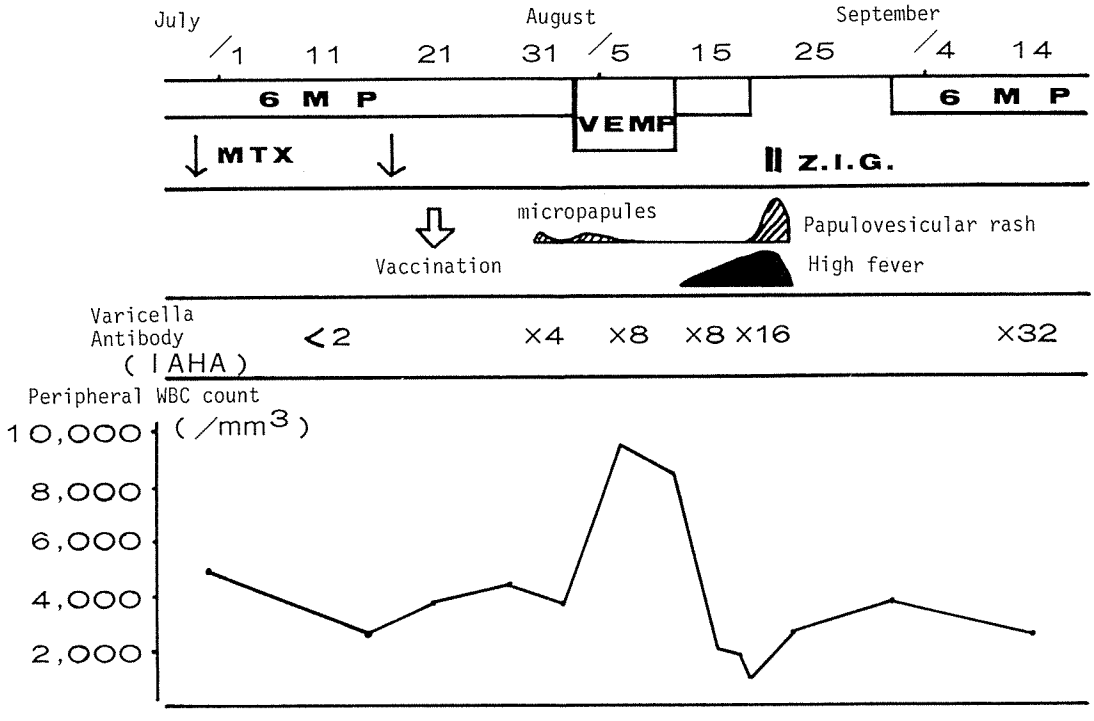

FIGURE 1

Asahikawa Medical College.

RESULTS

1. *Clinical responses*

The clinical responses after vaccination are presented in Table 1. Eight out of 10 patients had no fever and no skin rash. The other two patients developed mild fever and papulovesicular rash after vaccination.

A child with T-cell acute lymphocytic leukemia (Case 9) developed moderate varicella with high fever after vaccination as presented in Fig. 1. He exhibited a few countable papules 9 days after vaccination. 13 days after vaccination, he received intensive chemotherapy with Vincristine, Cyclophosphamide, 6-Mercaptopurine and Prednisolone. 22 days after vaccination, moderate varicella symptoms developed but no involvement of the lung was detected and he recovered completely.

Before varicella developed, the antibody titers of varicella-zoster virus had already increased. But the vaccine couldn't prevent varicella (probably because cellular immunity had been suppressed by intensive chemotherapy). Recently it has been reported that children with T-cell acute lymphocytic leukemia or malignant lymphoma often have a severe clinical response after varicella vaccination (Katsushima, 1983), so we must be careful in vaccinating such patients.

2. *Skin test reaction* (Table 2)

Skin test reactions with varicella virus antigen were performed. The reaction was called positive if the spot diameter was greater than or equal to 5 mm (Kamiya et al., 1977). All 9 patients on whom we performed skin tests showed a positive skin test reaction 1 month after vaccination. After that the skin test was performed repeatedly. 5 years after vaccination, one out of 3 patients showed a positive skin test reaction but 2 patients showed a negative skin test reaction after 5 years. It is known that the varicella skin test tends to show a negative reaction when leukemia relapses and recently these two patients relapsed from acute leukemia.

3. *Serological responses*

Serological responses were detected in 9 vaccinees. The antibody titers were rather low when compared with those of healthy children but persistence of neutralizing antibody was detected. Also in all 3 children who were

TABLE 2. *Vaccination and response*

Case No.	Skin test			Neutralizing antibody			
	0	1 mo	5 yr	0	1 mo	6 mo	4 yr
1	(−)	(±±)		<4	8	8	
2	(−)	(±)		<4[b]	<4	4	
3	(−)	(+)	(±)	<4[b]	<4[b]	<4[b]	4 → 8
4	(−)	(±)	(−)	<4	8	8	8
5	NT[a]	(+)		<4[b]	<4	4	
6	(−)	(+)	(−)	<4	4	8	8
7	(−)	(+)		<4	8	4	
8	NT	NT		<4[b]	4	8	
9	(−)	(±)		<2[c]	16[c]	32[c]	
10	(−)	(+)		NT	NT		

[a] Not tested.
[b] By complement fixation test.
[c] By immune adherence hemagglutination.

observed for more than 4 years, persistence of neutralizing antibody was detected as shown in Table 2.

CLINICAL EFFECTS OF VACCINATION

Figure 2 presents the clinical course of 10 children with leukemia. Patients labelled case 1, case 2, case 5, case 7 and case 10 died during the observation period, owing to relapse of acute leukemia and one patient owing to infection by Pneumocystis carinii.

These patients had several contacts with natural varicella in their schools or neighborhoods when they were in complete remission, however no clinical symptoms of varicella developed in spite of exposure to natural varicella.

Case 2 and case 7 had contact with natural varicella in the family, but they were free from symptoms of varicella.

Case 3 and case 8 were exposed to natural varicella when they relapsed and received many anticancer drugs after vaccination. Subsequently, mild fever and mild vesicular rash developed.

Figure 3 presents the clinical course of case 3. Case 3 is a child with acute lymphocytic leukemia who was vaccinated 4 years before. He was receiving anticancer drugs at this time for reinduction therapy. Immediately after discharge he was exposed to natural varicella. Two weeks after that, a papulovesicular rash developed but the rash was mild and he had no fever.

Case 8 is a child with acute leukemia who was vaccinated 1 year before. He had been receiving many anticancer drugs and craniospinal irradiation for treatment of meningeal infiltration as presented in Fig. 4. Immediately after discharge, he had contact with natural varicella in his family. After 2 weeks a mild papulovesicular rash developed on his chest. Neutralizing antibody increased from 4 fold to 8 fold but the number of the vesicles didn't increase, and he recovered completely. His general symptoms of varicella were mild.

Two patients were in severe immunosuppressive states as a result of chemotherapy and

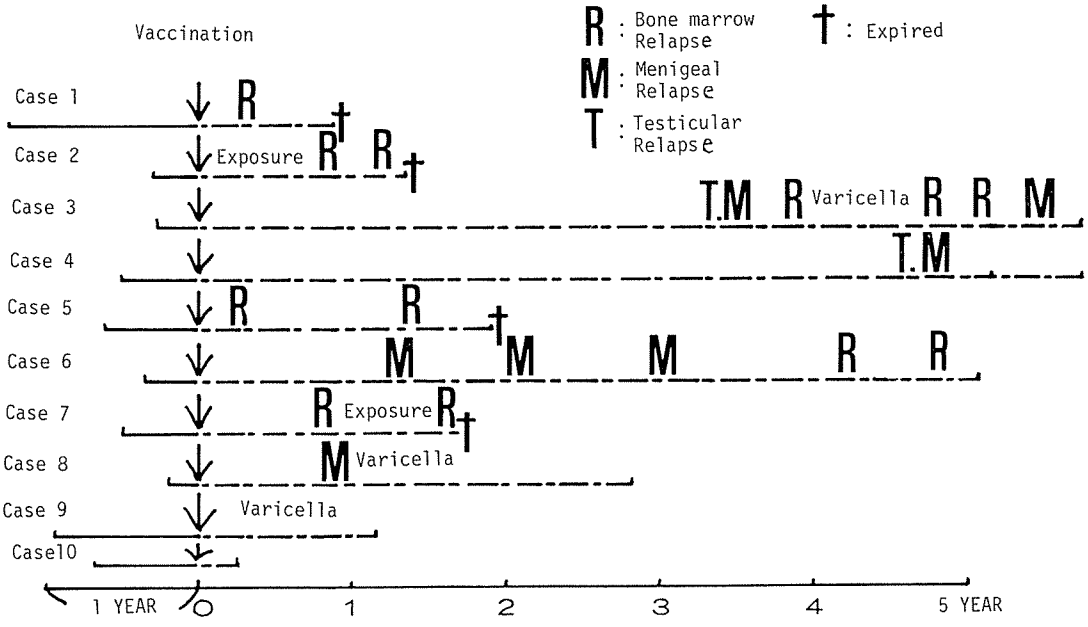

FIGURE 2

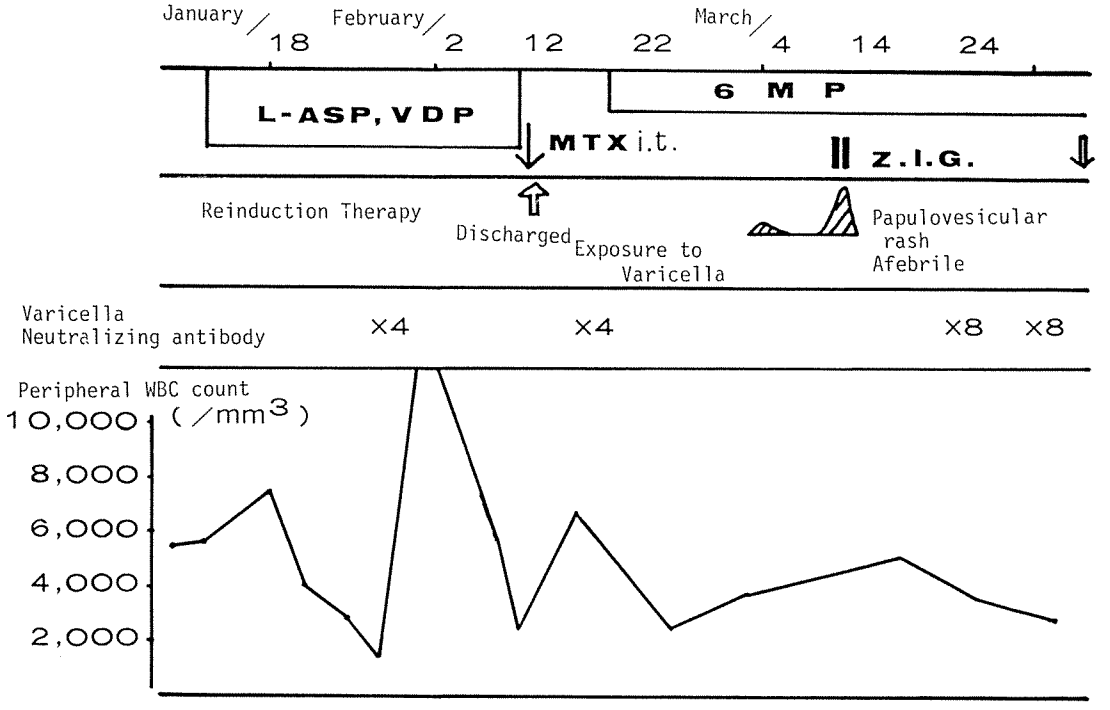

FIGURE 3

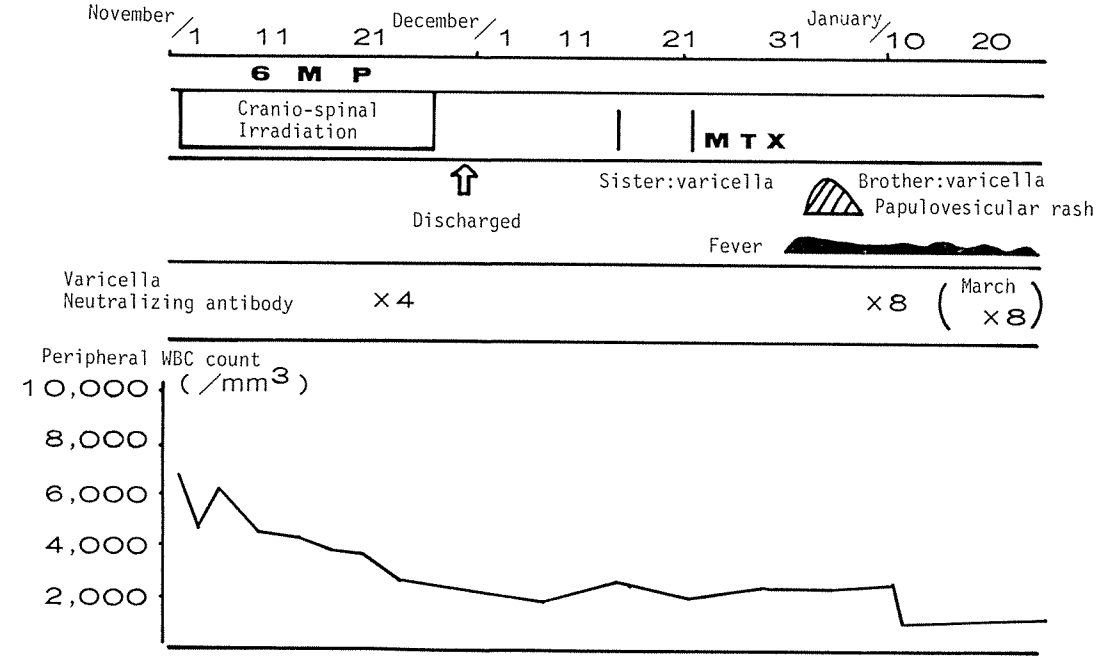

FIGURE 4

irradiation. Leukopenia had persisted in these cases, however their symptoms of varicella were mild. Past vaccination couldn't prevent the occurrence of varicella, but the symptoms of varicella were mild in spite of their immunosuppressive states.

It is considered from this experience that varicella vaccine sometimes cannot prevent varicella infection when the host is in an immunosuppressive state, but may prevent severe varicella symptoms as shown by these cases.

INCIDENCE OF HERPES-ZOSTER

None of the children developed herpes-zoster during the six year follow-up period. On the other hand, in a control group of children with leukemia who had a history of natural varicella, one patient out of seven developed herpes-zoster.

Table 3 presents reports by Sakurai (1982) and Yabuuchi (1983) about the incidence of herpes-zoster in children with leukemia. As Table 3 shows, vaccination of leukemic children didn't increase the incidence of herpes-zoster.

DISCUSSION

Since 1977, we have been using varicella vaccine to prevent severe varicella in patients with malignant diseases. As presented in Table 4, we vaccinated 10 children with leukemia, and 6 children with solid malignant tumors. Three children had clinical reactions after the vaccination and two out of 3 patients developed moderate varicella symptoms. One case was a child with T-cell acute lymphocytic leukemia as previously presented, and the other patient was a child with malignant lymphoma who had been receiving cranio-spinal irradiation.

From long-term observation, we consider that varicella vaccine is effective in clinical use and that most of the time it is "safe". Use of varicella vaccine does not increase the incidence of herpes-zoster and judging from the persistence of the neutralizing antibody, long term effectiveness can be expected.

We should however, be careful when vaccinating children with T-cell acute lymphocytic leukemia, malignant lymphoma and those who have received cranio-spinal irradiation.

It is also of great importance to continue research on the long-term effectiveness and safety of the varicella vaccine.

TABLE 3. *Incidence of herpes-zoster in children with acute leukemia*

Report \ Group	Incidence of herpes-zoster (Pt. with h-z/No. of pt.=(%))	
	History of varicella vaccine	History of natural varicella
Our study	0/ 9= 0	1/ 7=14.3
Sakurai	6/43=13.9	5/39=12.8
Yabuuchi	4/44= 9.1	8/37=21.6
Total	10/96=10.4	14/83=16.9

TABLE 4. *Recipient of varicella vaccine*

Disease	Case No.	Clinical reaction
Acute leukemia	10	2
Malignant lymphoma	3	1
Letterer-siwe	1	0
Neuroblastoma	1	0
Adrenocortical ca.	1	0

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