EXPERIENCE OF VARICELLA VACCINATION IN ACUTE LYMPHOPLASTIC LEUKAEMIA

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ABSTRACT

Varicella is a common benign childhood illness. Rarely, serious complications arise. Immunocompromised patients usually suffer a more serious form of the illness. It is therefore prudent to prevent the infection in this group of patients.

Varicella vaccination has been proven by several workers to be effective in both healthy children and adults as well as in leukaemic children.

As the vaccine had not been licensed far sale in Singapore, we could only import 10 doses af the vaccine under special license. This was given to 8 leukaemic children. Of this, 5 seroconverted after the first dose. Two patients had the benefit of a repeat vaccination 3 months later. Both subsequently seroconverted. Two of the patients died from a relapse of the illness, a year and 2 years after the vaccination.

None of the patients developed any side effects of fever and pain or varicella or zoster after the immunisation even though there was close contact with chicken pox.

Although the study sample was small, it appeared that the vaccine was safe and efficacious in leukaemic children, especially after a 2-dose injection.

Keywords: varicella infection, varicella vaccination, childhood acute lymphoblastic leukaemia

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INTRODUCTION

As one of the common childhood exanthems, varicella is not necessarily a benign condition. Even in healthy children complications like viral dissemination, bacterial infection, Reye's Syndrome and encephalitis occur. Beside the morbidity and occasional mortality, varicella also has an economic impact resulting from physician visits, loss of working days for the parents and loss of school days for the child.

In Singapore, between 1988 and 1990, 6 healthy people, including 2 children, 11 and 12 years of age, died from chicken-pox, giving a fatality rate of 0.11% [1]. In leukaemic children, 30% get visceral dissemination and 7% are at risk of dying [2]. Although anti-viral therapy and post-exposure prophylaxis with varicella zoster globulin have decreased the frequency of severe illness, these agents have their own limitations [3,4]. It makes more sense to prevent if possible, rather than to treat the illness.

Active immunisation of healthy and immunocompromised children have been studied by various workers in Japan, US and other parts of the world and most have found it to be favourable with few side effects [5-17].

The incidence of chicken-pox in Singapore has risen from 34.2/100,000 population in 1977 to 1826.8/100,000 population in 1993 [18] (Fig 1). With these startling numbers, leukaemic patients are obviously at an even greater risk of contracting the disease. Our own patients have had chicken-pox and zoster while undergoing therapy. Apart from the pain, systemic illness and the risk of disseminated illness, therapy also had to be suspended. This interruption in therapy may predispose the patient to a relapse. Fortunately, none succumbed to the infection.

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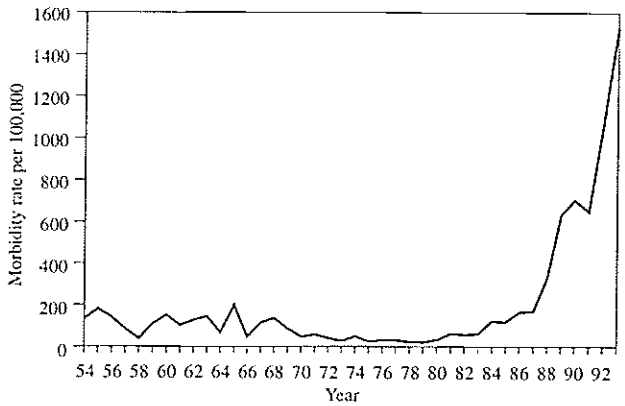
Fig 1 – Annual incidence rates of reported chickenpox cases in Singapore 1954-1993



Source: Communicable Disease Surveillance in Singapore, 1993
Quarantine & Epidemiology Department, Ministry of the Environment

In 1990, this vaccine had not been passed by the FDA in the United States. Similarly, it was not licensed for sale in Singapore by the Ministry of Health. It had to be imported under special license from Professor M Takahashi in the Research Institute for Microbial Disease, Osaka University. Only 10 doses of the OKA strain was available and this was airfreighted in and stored in the hospital pharmacy at 4 °C.

We report our experience with these 10 doses given to 8 patients with acute lymphoblastic leukaemia (ALL).

Patient selection

All the patients had ALL. Consent was obtained from the parents prior to the vaccination. A detailed history taken from the parents revealed that none of the patients has had varicella before. Preimmunisation serology by the enzyme linked method (EIA) was carried out in 6 of the patients and they were found to be negative. Based on these 2 criteria, the patients were assumed to be susceptible to varicella. Four of the patients were still on treatment while the other 4 had been taken off treatment for a period of 2 to 28 months prior to the immunisation.

Vaccination

The patients who were on chemotherapy were in the continuation phase of their treatment. Their schedule consisted of monthly pulse with Vincristine and a 5-day course of prednisolone, daily mercaptopurine and weekly methotrexate. Chemotherapy was suspended 1 week before and 1 week after the vaccination.

The vaccine (OKA strain, lot 018) containing 1000 pfu/dose was reconstituted just before the vaccination and patients were injected via the subcutaneous route.

The patients' lymphocyte count was more than 500/cmm at the time of the vaccination.

Patients were carefully monitored for side effects of fever, rash, and joint pains. Blood counts were checked and adverse effects like thrombocytopenia were noted as this had been reported as an adverse effect[14]. Details of exposure to chicken-pox either within the household, among neighbours or schoolmates were noted.

As only 2 doses were left after the first round, 2 patients received a second dose 3 months after the first vaccination.

Serology

Both the immunofluorescent test (IF) and EIA tests were done to confirm seroconversion. Serology was taken 6 weeks and 3 years after the vaccination to check the antibody status.

Tests for cell mediated immunity like skin testing and the lymphocyte stimulation tests were not done as it was not available then.

RESULTS

Altogether, 8 patients were vaccinated. Of these, 5 seroconverted (positive in both IF and EIA), giving a seroconversion rate of 62.5%. Of the 3 nonconverters, 2 (SKX,EGL) received a second dose 3 months after the first vaccination. Both subsequently seroconverted after the second dose (Table I).

None of the patients developed any pain or swelling over the injection site. Only one child had a mild flu-like illness. The rest did not have any fever nor rash which were the commonest side effects seen from other studies[9,19].

Two patients died from their disease. They were both high risk ALL (MR and LKA). MR had infantile leukaemia and LKA had high white count at presentation and was in third remission at the time of immunisation. Both relapsed a year later and died of the disease one year and 2 years after the vaccination. Death was not related to the vaccination.

The remaining 6 patients were followed up closely. None developed chicken-pox or zoster although all 6 were in contact with chicken-pox either directly within the household or with their neighbours and schoolmates. The incidence rate of chicken-pox in the local community was high with more than 1,000 cases per 100,000 population at that time (Fig 1).

Three years later, the antibody status was checked. This showed that 4 had remaining antibodies and 2 were negative. The latter received only one dose of the vaccine while the two who received the 2-dose vaccine remained seropositive. To date (5 years later), none of the 6 children alive has had chicken-pox nor zoster yet.

DISCUSSION

Varicella vaccine has been shown to be highly protective against chicken-pox in both normal and leukaemic children[5-17] with rates of seroconversion ranging from 96% to 98%[7] in normal children and 89% to 91% in leukaemic children[14,15]. Arbeter also found excellent immunologic response with the production of varicella antibodies and cellular response in 95% of normal children which were maintained for 5 years[17]. Takahashi also showed it to be useful in protecting susceptible children on steroids[20].

The incidence of zoster is low in normal healthy children[24]. In a group that had been vaccinated, the incidence of zoster had not been shown to be increased[21]. In leukaemic children, about 10% get zoster[22]. The American studies carried out by the NIAID showed that the incidence of zoster was lower in the vaccinated patients (2%) as compared to the controls (15%)[23].

In Gershon's series, none of the vaccinated leukaemics developed zoster while 21% of the controls did[9,23-28].

Side effects consisted mainly of a low grade fever and a maculopapular rash in 10% of the patients[19]. Disseminated varicella has not been reported. Secondary cases in a sibling following vaccination occurs in about 15% of cases[15]. These cases occur usually when the vaccinee develops skin lesions and

Table I – Varicella zoster virus antibody status of the eight patients with acute lymphoblastic leukaemia.

	Sex	Age	Treatment status	Immune status	6 weeks IF	6 weeks EIA	Post 2nd dose vaccination IF	Post 2nd dose vaccination EIA	3 years EIA	Remarks
SKX	M	7 years	Off x 28 mo	not done	–	–	+	+	+	Contact with schoolmates
AC	F	9 years	Off x 22 mo	not done	+	+	–		–	Contact with siblings
LLG	M	7 years	Off x 24 mo	not done	+	+	–		+	Contact with neighbours and schoolmates
MR	M	3 years	Off x 2 mo	Negative	+	–				Died in first relapse
LSH	M	9 years	On	Negative	+	+	–		–	Contact with schoolmates and neighbours
TCC	M	10 years	On	Negative	+	+	–		+	Contact with schoolmates and neighbours. Relapse leukaemia 2 years later
EGL	F	7 years	On	Negative	–	–	Vaccinated +	+	+	Contact with schoolmates and neighbours
LKA	M	9 years	On	Negative	–	–				Died in relapse

IF: Immunofluorescene EIA: Enzyme immunoassay

these varicella infections have all been noted to be mild. Sometimes even tertiary [29] transmissions to the siblings have been reported [15,24,25]. There is no apparent increase in the incidence of relapse in vaccinated patients [15]. It would appear therefore that this vaccine is safe.

Leukaemic children are immunocompromised and very susceptible to this infection. The mortality and morbidity is high and hence it would make sense to vaccinate these children.

Owing to the status of the licensure of the vaccine in Singapore, we only had 10 doses of the vaccine and hence only a very small number of patients were vaccinated. Of the 8 patients, 5 seroconverted after the first dose (62.5%) and another two converted after the second dose, giving an overall rate of 75%. These levels are low as compared to similar studies by Gershon [14] and Arbeter [15] who obtained seroconversion rates of 89% to 91% respectively. Similarly, seroconversion rates of 96% to 98% were achieved in healthy patients [7,16], after a single dose vaccine. However, in Arbeter's study, the population were children who had been off therapy for 6 months. In our group, half of the patients were still on chemotherapy which depresses the body's immune response. This may explain the lower rate of seroconversion. As with other studies, it was found that immune-compromised patients will require 2 doses of vaccination to achieve maximum protection [9,30].

Serological conversion only indicates the presence of humoral immunity. All three - humoral, cellular and secretory immunity [31-33] are necessary for the protection against the varicella virus [8]. Most studies used humoral immunity to assess protection and it is the most frequently studied. Cellular immunity [26] is important but not as extensively studied. Less so is the secretory immunity elicited by the varicella vaccine [5].

Some series have detected persistence of antibodies in at least 94% of healthy children 2 to 4 years post-vaccination [27]. Kuter found that antibody persisted in 100% of the children tested 6 years after vaccination and 55 of the 463 vaccinees developed varicella during the 7-year follow-up. There was no increase in the incidence of varicella over time [28]. In leukaemic children, 20% of seropositive vaccinees become seronegative after 1 year and over the next 5 years, this rate remains fairly constant [26]. Subclinical infections resulting in an increase of the varicella antibody titre can occur in seronegative patients who remain asymptomatic after household exposure to varicella [19]. This subclinical infection is theorised to play a key role in the maintenance of long-term immunity [34].

Our patients were carefully monitored and parents were questioned closely on their children's possibility of having chicken-pox. Parents in fact were very aware of the fact that the children could possibly get chicken-pox despite the vaccination. Throughout this whole period, there was no clinical evidence to suggest that these children had any evidence of chicken-pox although some of them had close household contact. At the point of contact, perhaps serological testing could have been done to detect a rise in the antibody titre. This was not done as the children already had considerable needle phobia and were reluctant to have any further blood tests done on them.

In our own cohort, 2 patients lost their seropositivity and despite exposure to varicella (AC) in her siblings and (LSH) in his schoolmates and neighbours, neither developed clinical infections. Subclinical infections, if it occurred did not enhance their serological markers. They both became seronegative.

The most important indicator of immunity is the degree of protection provided to the vaccinees following exposure to the varicella virus. Here, cell mediated immunity must have contributed to their protection. To exemplify this, Baba et al [35] in his study on institutionalised infants and varicella infections found that all individuals with negative skin test to varicella antigen before a varicella outbreak developed clinical chicken-pox, and pre-existing antibodies did not prevent the development of the illness although the severity was milder in those with a higher antibody titre.

In another paper by Takahashi [20], varicella vaccine was given to 18 susceptible children. All these had the positive conversion on skin testing with varicella virus antigen with little pre-existing humoral antibody. These children were all protected against a clinical varicella epidemic which subsequently occurred in that institution.

Unfortunately, the test for cell mediated immunity were not done for our patients as it was not available in the institution at that time. If it had been done, the results may have supported our hypothesis that cell mediated immunity had contributed to their protection.

As stated earlier, about 10% of vaccinees get a low grade fever and a mild maculopapular rash. Also, some reports have cited thrombocytopaenia as another side effect [19]. Only one of the patients had a mild flu-like illness. He recovered very quickly. None had attenuated varicella infection as an immediate effect, or zoster up till the present moment which is 5 years after the immunisation. There were no adverse effects on the haematological parameters.

Like other workers, we found that varicella vaccine can be safely given with efficacy in this group of immune-compromised patients. However, this study group was small owing to the constraints of the licensure of the vaccine and the prohibitive cost. A much larger series with tests to check on cell mediated immunity will certainly be of much value to confirm the safety and efficacy of the vaccine.

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REFERENCES

1. Lam MS, Chew SK, Allen DM, Monteiro EHA. Fatal varicella infection in Singapore. Singapore Med J 1993; 34; 213-5.
2. Feldman S, Hughes WT, Daniel CB. Varicella in children with cancer. Pediatrics 1975; 56:388-97.
3. Prober CG, Kirk LE, Keeney RE. Acyclovir therapy of chicken-pox in immunocompromised children - a collaborative study. J Paeds 1982; 101: 622.
4. Zaia JA, Levin MJ, Preblud ST, et al. Evaluation of varicella immunoglobulin protection of immunosuppressed children after household exposure to varicella. J Infect Dis 1983; 147: 737-43.
5. Weibil RE, Kuter BJ, Neff BJ, Rothenberger CA, Fitzgerald AJ, Connor KA, et al. Live OKA/Merck varicella vaccine in healthy children. JAMA 1985; 254:2435-9.
6. White CJ, Kuter BJ, Hildebrand CS, Isganitis KL, Miller WJ. Varicella vaccine (Varivax) in healthy children and adolescents: results from clinical trials, 1987-1989. Pediatrics 1991;87:604-10.
7. Weibel R, Neff BJ, Kuter BJ, Guess HA, Rothenberger CA, Fitzgerald AJ. Live attenuated varicella virus vaccine efficacy trial in healthy children. N Engl J Med 1984; 310:1409-15.
8. Gershon AA. Viral vaccines of the future. Pediatric Clin North Am 1990; 37: 689-707.
9. Gershon AA, LaRussa P, Hardy I, Steinberg S, Silverstein S. Varicella vaccine, the American experience. J Infect Dis 1992; 166(suppl 1): S63-8.
10. Watson BM, Piercy SA, Plotkin SA, Starr SE. Modified chicken pox in children immunised with OKA/Merck varicella vaccine. Pediatrics 1993; 91:17-22.

11. Gershon AA, Steinberg SP, Gelb L. Live attenuated varicella vaccine: efficacy for children with leukaemia in remission. JAMA 1984; 252: 355-62.

12. Ridgway D. Wolff LJ. Active immunisation of chicken pox with leukaemia and other malignancies. Leukaemia and Lymphoma. 1993; 9(3): 177-92.

13. White CJ, Kuter BJ, Ngai A, Hildebrand CS, Isganitis KL, Patterson CM, et al. Modified cases of chicken pox after varicella vaccination: correlation of protection with antibody response. Ped Infect Dis 1992; 11(1): 19-23.

14. Gershon AA, Steinberg SP, Gelb C. Live attenuated varicella vaccine in immunocompromised children and adults. Pediatrics 1986; 78(4)suppl: 757-62.

15. Arbeter AM, Granowetter L, Starr SE, Lange B, Wimmer R, Plotkin SA. Immunisation of children with acute lymphoblastic leukaemia with live attenuated varicella vaccine without complete suspension of chemotherapy. Pediatrics 1990; 85(3):338-44.

16. Kuter BH, Weibel RE, Guess HA, Matthews H, Morton DH, Neff BJ. OKA/Merck varicella vaccine in healthy children: final reassessment of a 2-year efficacy study and 7-year follow up studies. Vaccine 1991;9:643-7.

17. Arbeter AM, Starr SE, Plotkin SA. Varicella vaccine studies in healthy children and adults. Pediatrics 1986; 78(suppl): 748-56.

18. Communicable Disease Surveillance in Singapore 1993. Quarantine and Epidemiology Department, Ministry of Environment, 1993.

19. Plotkin SA. Varicella vaccine. Pediatrics 1986; 78(4): 765-70.

20. Takahashi M. Clinical overview of varicella vaccine: development and early studies. Pediatrics 1986; 78(4): 736-41.

21. White CJ. Varicella vaccine reflux. Reply. Pediatrics 1992;89:354.

22. Gershon AA. Live attenuated varicella vaccine. J Pediatrics 1987;110(1):154-7.

23. Lawrence R, Gershon AA, Holzman R, Steinberg S. NIAID Varicella Vaccine Collaborative study group. The risk of zoster after varicella vaccine in children with leukaemia. N Engl J Med 1988; 318:543-8.

24. Hardy IB, Gershon AA, Steinberg S, LaRussa P. NIAID Collaborative Varicella Vaccine study group. The incidence of zoster after immunisation with live attenuated vaccine. A study in children leukaemia. N Engl J Med 1991;325:1545-50.

25. Drwah-Klein LA, O'Donovan LA. Varicella in pediatric patients. Annals of Pharmacotherapy 1993;27:938-48.

26. Plotkin SA, Starr SE, Conner K, Morton D. Zoster on normal children after varicella vaccine. J Infect Dis 1989;159:1000-1.

27. Takahashi M, Kamiya H, Baba K, Asano Y, Ozaki T, Horiuchi K. Clinical experience with Oka live varicella vaccine in Japan. Postgraduate Med J 1985;61(Suppl 4):61-7.

28. Brunell PA, Taylor-Wiedman J, Geiser CF, Frierson I, Lydick E. Risk of herpes zoster in children with leukaemia: varicella vaccine compared with history of chicken pox. Pediatrics 1986;77(1):53-6.

29. Tsolia M, Gershon AA, Steinberg SP, Gelb L. NIAID Varicella Vaccine Collaborative Study Group. Live attenuated varicella vaccine: evidence that the vaccine is attenuated and the importance of skin lesions in transmission of varicella zoster virus. J Pediatrics 1990;116:184-9.

30. Gershon AA, Steinberg PS, Gelb L. NIAID Varicella Vaccine Collaborative Study Group. Pediatrics 1986;78(4) suppl:757-62.

31. Arvin AM. Cell mediated immunity to varicella zoster virus. J Infect Dis 1992; 166(suppl):S35-41.

32. Johnson C, Rome LP, Stancin T, Kuma HL. Humoral immunity and clinical reinfection following varicella vaccine in healthy children. Pediatrics 1989; 84:418-21.

33. Gershon AA, Sternberg SP. Varicella Vaccine Collaborative Study Group of the National Institute of Allergy & Inf. Diseases. Persistence of immunity to varicella in children with leukaemia immunized with live attenuated varicella vaccine. N Engl J Med 1989; 320:892-7.

34. Asano Y, Nagai T, Miyata T, Tazaki T, Ito S, Yamanishi K, et al. Long term protective immunity of recipients of the OKA strain of live varicella vaccine. Pediatrics 1985;75:667-71.

35. Baba K, Yabuuchi H, Takahashi M, Ogra PL. Immunologic and epidemic aspects of varicella infection acquired during infancy and early childhood. J Ped 1982;100:881-5.