BIKEN JOURNAL Vol. 27, 83–88, 1984

ADMINISTRATION OF VARICELLA VACCINE TO CHILDREN WITH LEUKEMIA

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INTRODUCTION

Varicella has been reported to be fatal in 7% of children with acute lymphocytic leukemia (ALL) and cause life threatening illness in approximately one third of cases (Feldman et al., 1975). Recent estimates, possibly because of more intensive chemotherapy, suggest that the mortality rate may be twice that cited earlier (Arvin et al., 1982; Prober et al., 1982; Whitley, 1982). In order to prevent varicella in these children, passive immunization with zoster immune globulin (ZIG) was developed (Brunell et al., 1972). This method of intervention required recognition of exposure and prompt administration of ZIG. In addition, each subsequent exposure of a susceptible required reimmunization.

Initial reports indicate that the administration of live varicella vaccine (LVV) to children with ALL was reasonably well tolerated, and that antibody responses were adequate, though poorer than in normal children (Izawa et al., 1977). Subsequently, studies were undertaken to immunize children with ALL starting with those in remission who had completed their chemotherapy. Those children in remission who were receiving maintenance chemotherapy were immunized, with suspension of chemotherapy for one week prior to and one week following immunization (Brunell et al., 1982). The time between diagnosis of leukemia and immunization was gradually shortened until the interval which failed to produce an adequate serologic response was established. We will review the status of these studies.

METHODS

Children with ALL who were cared for at the Children's Cancer Center in San Antonio or at M.D. Anderson Hospital in Houston were tested by fluorescent antibody against membrane antigen (FAMA) for antibody against varicella (Williams et al., 1974). Those who were devoid of antibody at a 1:2 level were eligible for the study. The study protocol was reviewed with the parents of the children and, where appropriate, with the children themselves. Those wishing to participate provided a signed statement of informed consent. Blood samples were obtained from the vaccinees at the time of immunization, 10–16 days post immunization (p.i.) and 30 days, 6 months, and yearly following immunization. If necessary, additional specimens were obtained. Samples were tested for antibody by FAMA.

Children in remission were inoculated subcutaneously with 550 to 700 PFU of the Oka strain of LVV. Chemotherapy was suspended for one week prior to and an aditional week post immunization. Vaccinees were observed for rash and temperatures were recorded twice daily from the 7th to 21st day p.i. Exposutes to varicella or zoster or the develop-

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ment of zoster were to be reported to us. Queries concerning exposures or development of zoster were made at each revisit. If vaccinees failed to respond or lost antibody, they were reimmunized.

All vesicular lesions were sampled and the material examined by electron microscopy or added to cultures of human embryonic lung fibroblasts (HELF) and observed for cytopathic effects. Cultures were also inoculated with specimens of urine, pharyngeal secretions or buffy coat obtained on two separate occasions between 10–16 days p.i.

At the time of immunization and six weeks subsequently, blood was obtained from all household members. Serum was tested for Varicella-zoster (V-Z) antibody to determine whether there had been rises in V-Z antibody titer since immunization.

LABORATORY TECHNIQUES

The method for determining antibody by FAMA has been described previously (Williams et al., 1974). Lymphocyte stimulation was performed as described previously (Brunell et al., 1982), using lymphocytes which had been isolated from peripheral blood. Multiple dilution of V-Z antigen were added to lymphocytes, 10^6 per ml, in RPMI 1640 containing 17% AB positive serum from a single V-Z immune donor. After incubation for 6 days ^3H thymidine was added to the cultures. After 6 h, an automatic harvester was used to extract the radioactive thymidine incorporated into the lymphocytes. Radioactivity was determined using a scintillation counter. The stimulation index (SI) was defined as the counts per minute produced by lymphocytes cultured with V-Z antigen divided by that produced by cells cultured with uninfected HELF.

RESULTS

Protective effect of immunization

Twelve patients were immunized following cessation of chemotherapy; 17 were receiving maintenance chemotherapy, but were at least a year since diagnosis; 15 patients were between 6 months and a year following diagnosis. SI were found to increase in all but 2 vaccinees within 30 days p.i. In many instances, however, values fell to preimmunization levels within 1–2 years p.i. Although a SI of 3 was used to separate immunes from susceptibles, as defined by ELISA (Shehab and Brunell, in preparation), some subjects had slightly higher levels at the time of immunization. There were not significant differences in the responses of the three groups of vaccinees (Table 1).

All but 1 of 28 children who received vaccine more than one year following diagnosis of leukemia responded to vaccine as defined by the development of a FAMA value of 1: 2 or greater. Three of 15 vaccinees immunized while on chemotherapy for more than a year lost antibody at 6 months p.i. Two additional vaccinees in this group and 1 child who had completed chemotherapy lost antibody at 2 and 3 years p.i., respectively (Table 2). Those immunized within a year post diagnosis had lower antibody levels and the response was often delayed beyond 30 days. Only 9 of 16 of these children responded to immunization. What is more, one of the 9 who responded failed to maintain immune levels of antibody for more than 6 months.

Five of 6 children who failed to respond or lost their protective level of antibody were reimmunized successfully; one child who was immunized twice failed to respond both times. The most critical measure of protection is the effect of exposure to varicella or zoster. The outcome of household exposure is more predictable than, and has a higher attack rate than non-household exposure. None of the 22 non-household exposures resulted in cases of varicella while 2 of 9 household exposures resulted in cases. Only 1 of the exposures was to zoster; a household exposure that did not result in a case.

One child who had completed chemotherapy developed only 6 vesicular lesions following exposures to a sibling. A second child who received vaccine while receiving chemotherapy after more than a year since diagnosis developed only 12 maculopapular lesions following a similar exposure. Both developed brisk antibody responses following infection. One had a FAMA of 1: 2 and the other 1: 16 just prior

TABLE 1. *Lymphocyte stimulation[a] index of varicella vaccine recipients*

	Duration since immunization in months						
	0	1	6	12	24	36	48
Completed chemotheraphy	1.2 (12)	14.6 (10)	8.1 (8)	6.4 (12)	11.3 (11)	32.6 (6)	82.3 (1)
Chemotherapy suspended							
More than 1 year since diagnosis	2.5 (16)	14.1 (15)	8.6 (14)	14.6 (10)	6.0 (5)	14.2 (2)	
6–12 months since diagnosis	2.9 (11)	12.1 (9)	12.9 (8)	15.2 (2)			

Numbers in parenthesis indicate number of observations.

[a] Stimulation index $= \frac{\text{cpm viral antigen}}{\text{cpm control antigen}}$

TABLE 2. *Antibody status of varicella vaccine recipients*

	Duration since immunization in months					
	0	1	6	12	24	36
Completed chemotherapy	0/12	12/12	12/12	12/12	10/10	4/5
Chemotherapy suspended						
More than 1 year since diagnosis	0/17	15/16	12/15	11/12	5/7	2/2
6–12 months since diagnosis	0/15	9/16	7/8	3/3		

to exposure. Their SI at this time were 1.4 and 4.1, respectively.

ADVERSE REACTIONS

Six children received vaccine three years previously, 15 two years previously, and 26 more than a year previously, and none have developed zoster. Two children developed areas of erythema at the site of injection about one week p.i. The lesions were about 3 cm in diameter, lasted about 2 days and were accompanied by only minimal discomfort. Two children, one of whom developed a vaccine associated rash and generalized lymphadenopathy, had elevations of temperatures of 1 C that could not be explained except to attribute it to vaccine. The fever lasted about 3 days and occurred about 2 weeks p.i.

Five children developed maculopapular erythematous rashes on the face and upper trunk 4–12 days p.i. Three of these children and two additional children developed vesicular rashes on an erythematous base 14 to 23 days p.i. Virus was isolated from vesicular fluid obtained from one of these vaccinees on the 26th and on the 28th day p.i. This was shown to be vaccine like by restriction enzyme analysis. (Brunell and Cobb, in preparation). Virus was demonstrated by electron microscopy in vesicular fluid obtained from another patient. A sibling of the latter patient, who was seronegative, was found to have antibody in the immune range when tested 6 weeks p.i. The child had no known exposure to zoster or varicella and developed no clinical signs of illness. This was the only one of 36 susceptible contacts who seroconverted. None of the 96 immune contacts had a significant rise in antibody.

V-Z virus was not isolated from the urine, pharyngeal secretions or buffy coat obtained from any of the patients 10–16 days p.i. Cytomegalovirus (CMV) was recovered from the

urine of 4 of these children. CMV also was found in the white cells and pharynx of one of these four children. None of the children from whom CMV was isolated had illness attributable to this virus.

COMMENT

LVV produces minimal morbidity and appears to protect against serious varicella infection in children with ALL. None of the 22 non-household exposures resulted in cases of varicella. The outcome of this type of exposure is unpredictable (Orestein et al., 1981). Of greater importance is the finding that only 2 of 9 vaccinees had clinical evidence of very modified varicella following household exposure, in comparison to severe illness in about half and death in about 15 percent reported in unimmunized children with ALL who developed varicella (Arvin et al., 1982; Prober et al., 1982; Whitley et al., 1982). Indeed healthy children experience an attack rate of approximately 90% following an introduction of varicella into their household. These children usually experience 100–250 vesicular lesions (Ross, 1962) while our 2 vaccinees had only 6 and 12 lesions.

The appearance of any vesicular lesions in children with serum antibody at the time of exposure is at variance with our prior experience in normal children (Williams et al., 1974; Brunell et al., 1975). Reinfection of normals has been documented, but in the absence of clinical illness (Brunell et al., 1975). Children with ALL, however, may have defective cell mediated responses which might have permitted the expression of clinical illness. Both vaccinees have relatively a very low SI just prior to exposure. Rises in the SI tend to be relatively transitory following immunization of children with ALL with LVV. Serum V-Z antibody tends to be more durable, but also may fall below the immune range.

Spread of vaccine virus occurred in one instance. The sibling who seroconverted failed to develop clinical illness, as would be likely, following the infection of normal children with LVV (Takahashi et al., 1974). The spread to immunocompromised children, however, is potentially hazardous particularly if they are in the intensification phase of therapy when they might be expected to be most immunocompromised. The finding that virus isolated from the vesicular lesions retains its vaccine like characteristics rather than reverting to wild type, which might be expected to be more virulent, is reassuring. As a precaution we isolate vaccine recipients from other children with malignant disease for one month p.i., even though the chances of spread appear to be small. The failure to isolate virus from the vaccinees confirms the low likelihood of contagion; virus is not usually recoverable from the respiratory secretions of normal children with chickenpox (Gold, 1966; Nelson and St Geme, 1966).

The failure to observe zoster in our vaccinees is at variance with the experience of Japanese investigators who report an incidence of approximately 10% in children with ALL who received LVV (Takahashi et al., 1981). Approximately 14 percent of our population of children with ALL who have had natural varicella developed zoster (Brunell et al., 1982). Our findings suggest that zoster is no more common in children who receive vaccine than those who have had natural varicella. Careful analysis of the two groups of children with ALL with respect to duration since V-Z infection will be necessary to define the risk with certainty.

The morbidity produced by LVV is minimal and certainly is preferable to the consequences of unprotected varicella in these patients. The reactions at the site of inoculation appeared one week p.i. and were probably immunologically mediated. At 10 days p.i. vaccinees generally had serum V-Z antibody. The early rash generally appeared about the same time. Neither of these reactions was clinically significant. The late rash probably represented aborted varicella as virus could be demonstrated in the lesions of 2 of the vaccinees.

Again these reactions were mild and the only adverse result was the spread of virus to the contacts of 1 of the vaccinees.

LVV appears to provide an effective and safe method of preventing severe varicella in children with ALL. At the present time it would appear as though active immunization could be accomplished successfully as early as one year after the diagnosis of ALL. Immunization prior to this time does not appear to yield as good an immune response as antibody production is delayed, titers are lower and responses are often transitory. An alternative to active immunization would be desirable to protect children prior to the time LVV can be given. Passive immunization post exposure has been effective in reducing morbidity from varicella in ALL (Brunell et al., 1972). Our current program is to give VZIG at regular intervals until active immunization can be accomplished. The observation that children given plasma containing platelets raises their V-Z antibody titer about as effectively as administration of VZIG (Shehab and Brunell, in preparation) suggests that some form of intravenous globulin may be an effective method of preventing varicella morbidity prior to the time that active immunization can be accomplished.

ACKNOWLEDGMENTS

This work was supported by a grant (2 RO1 AI15492-05) from the National Institutes of Allergy and Infectious Diseases.

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