ORIGINAL ARTICLE

Varicella In Children With Haematological Malignancy – Outcome Of Treatment And Prevention

C.M.L. Ho, MRCP*
R. Khuzaiah, MRCP*
A.M. Yasmin, MRCPath**
* *Department of Paediatrics, Hospital Besar, Kuala Lumpur.*
** *Department of Microbiology, National University of Malaysia, Kuala Lumpur.*

Summary

Primary varicella-zoster virus infection in children with haematological malignancy is a life threatening disease. In one year, there were 10 cases of varicella and 2 cases of zoster among these children as well as 5 mothers who were accompanying their children who developed varicella in the oncology ward. Two children died of fulminating disease despite aggressive antiviral and supportive treatment. Acycloviar can be used in treatment and prophylaxis in exposed susceptible children. Varicella -zoster immune globulin is not available in this country. Vaccination with live virus has been shown to be protective in immunocompromised children and needs consideration.

Key words: Varicella, Acyclovir, VZIG, Varicella vaccine, Malignancy.

Introduction

Varicella or chickenpox and herpes zoster are caused by Herpesvirus varicellae. Varicella is the primary disease of a non-immune host. The virus then becomes latent in the ganglion of nerve cells, both sensory and motor. It can be reactivated in the host as herpes zoster when the cell mediated immunity and neutralising antibodies are unable to keep it under control. It can be reactivated by trauma, stress, malignancy, immunosuppressive drugs or radiation. It is accepted that primary varicella infection is an innocuous exanthem of childhood. Mortality in normal children is 0.0014%, but in the immunocompromised children, it is associated with dissemination and a mortality of 6 to 17% [1,2]. In the immunocompromised children, apart from severe skin manifestation, visceral involvement causing pneumonitis, hepatitis, pancreatitis, encephalitis, myocarditis and disseminated intravascular coagulation may occur.

Varicella is very infectious and spreads by droplets from mouth and nose as well as from vesicular fluid. The incubation period is 11-21 days and infectivity is from 24 hours before rash till all the lesions are crusted. The attack rate ranges from 80-90% for household contacts, 68% for hospital contacts and 46% in open society[4].

This paper is a review of cases of varicella in children with malignancy from 1/1/92 - 31/12/92 in the government paediatric haematology and oncology ward in the Paediatric Institute, General Hospital Kuala Lumpur. The aim is to review:-

a) spectrum and severity of varicella in children with malignancy
b) outbreaks in the ward and management of the patients.

Patients and methods

Medical records of all patients with varicella infection were reviewed in the stated period. There were 10 cases of disseminated varicella. Six cases were acquired in the ward (but 1 developed the disease after discharge) and 4 cases at home. The records were reviewed for underlying disease, stage of treatment, clinical manifestations, white blood counts, renal and liver function tests and outcome. In addition, there were 2 patients with herpes zoster and 5 mothers accompanying their children also developed varicella. Severity of varicella infection was graded as in (Table I).

Table I
Grading of severity of organ involvement[2]

Severity	+	++	+++	++++
Skin	Mild < 10 Vesicles	Moderate 10-50 Vesicles	Severe >50 Vesicles	
Hepatitis	SGPT > 100 U/L	SGPT > 250 U/L	SGPT > 2500 U/L	
Encephalitis	Lethargy	Altered Consciousness	Fits	Severe Depression of Consciousness
Pneumonitis	Tachypnoea	Tachypnoea + Infiltrates	Extensive Infiltrates+ Oxygen Requirement	Ventilatory Support

Results

There were 10 children (ages from 4 to 11 years) who developed varicella infection during the review period. Seven were diagnosed to have Acute Lymphocytic Leukaemia (ALL), 2 with Acute Myeloid Leukaemia (AML) and 1 with Chronic Granulomatous Leukaemia (CGL). Patient characteristics and details of cytotoxic chemotherapy are shown in Table II. All the patients except patient no. 6 were treated with IV Acyclovir (ACV) 500mg/m^2 8 hourly for 10 days. This patient developed varicella infection 6 days after discharge.

The severity of the varicella infection by organ involvement and their outcome is shown in Table III.

The majority of patients (7/10) had severe skin manifestation. Only patient no. 4 had < 5 vesicles but he was a new case and cytotoxic treatment had not been started yet. Five cases had hepatitis and 4 of them had SGPT levels > 1000 U/L. The diagnosis of encephalitis in the patients was made on clinical ground. Two presented with lethargy and another 2 had altered consciousness. There were 4 patients with pneumonitis of which 3 required ventilation. The 2 patients who died had severe pneumonitis.

Table II
Children with varicella infection - patient characteristic, treatment stage, initial white blood counts and outcome

Case/Age (Yr)/Sex	Diagnosis	Treatment Stage	Initial Lymphocyte Cells/Mm^3	Initial Neutrophil Cells/Mm^3	Rx. ACV	Outcome
1/5/M	ALL	Maintenance (6MP,MTX,VCR,P)	800	700	Y	Survived
2/8/M	ALL	Consolidation (VP16,AraC,DXT)	700	200	Y	Died
3/5/F	ALL	Maintenance	800	5300	Y	Survived
4/6/M	ALL	New Case (no chemo)	6100	400	Y	Survived
5/7/M	AML	Relapse (DNR,AraC,P)	900	1400	Y	Survived
6/10/M	CGL	Maintenance (Hydroxyurea)	3500	1600	N	Survived
7/4/M	ALL	Consolidation	1000	600	Y	Survived
8/11/M	AML	Induction (DNR,AraC,P)	0	4100	Y	Died
9/8/M	ALL	Maintenance	500	4000	Y	Survived
10/5/M	ALL	Maintenance	500	4000	Y	Survived

M=Male, F=Female, Y=Yes, N=No, ACV=Acycloviar, 6MP=6-Mercaptopurine, MTX=Methotrexate, VCR=Vincristine, P=Prednisolone, DNR=Daunorubicin, AraC=Cytosar, VP16=Etoposide, DXT=Cranial Irradiation, chemo=Chemotherapy.

Table III
Severity of varicella infection and outcome

Case	Skin	Hepatitis	Pneumonitis	Encephalitis	Outcome
1	Severe	+++	–	–	Survived
2	Severe (H)	+++	++++	++	Died
3	Moderate	–	–	–	Survived
4*	Mild	–	–	*	Survived
5	Severe (H)	+++	+	+	Survived
6	Severe	?	–	–	Survived
7	Mild	–	–	–	Survived
8	Severe (H)	–	++++	+	Died
9	Severe (H)	+++	++++	++	Survived
10	Severe	++	–	–	survived

**Patient 4 was a new case of ALL who presented with bilateral optic neuritis and change in sensorium. He developed varicella on 5th day of admission. Varicella encephalitis could not be excluded. Lumbar puncture examination was inconclusive.*

(H) = haemorrhagic vesicular fluid. The various degrees of involvement are explained in the section on Patients and method.

Table IV shows 5 children whose mothers developed chicken pox. The children were all given ACV as prophylaxis, 2 were given intravenously and 3 given orally for average of 1 week. None of them developed varicella infection. All of the children were on cytotoxic therapy but had good absolute lymphocyte counts. Patient B died of protracted diarrhoea but there was no evidence of varicella.

Table V shows the details of the 2 children with zoster. They were both given IV ACV for 10 days and recovered. Both were on maintenance therapy when they developed zoster. They had localised dermatomal lesions only.

Table IV
Children with mothers who developed chickenpox - patient characteristic, initial white blood counts, treatment and development of variella

Case/Age (Yr)/Sex	Diagnosis	Treatment Stage	Initial Lymphocyte Cells/Mm^3	Initial Neutrophil Cells/Mm^3	Treatment ACV	Varicella Infection
A/1/M	Lch	Induction (P, VP16)	3200	5600	Iv	No
B/0.7/F	Lch	Induction	3800	1500	Oral	No
C/6/M	Aml	Induction (P,VCR,ADR AraC)	2000	100	Oral	No
D/2/F	Aml	Induction (P,VCR,ADR AraC)	4500	300	Oral	No
E/2/M	All	Induction (P,VCR,DNR L-ASP)	2000	400	Iv	No

LCH=Langerhan Cell Histiocytosis, AML=Acute Myeloid Leukaemia, ALL=Acute Lymphoblastic Leukaemia, IV=Intravenously, P=Prednisolone, VCR=Vincristine, DNR=Daunorubicin, L-ASP=L-Asparaginase, AraC=Cytosar, ADR=Adriamycin, VP16=Etoposide.

Table V
Children with zoster infection - patient characteristic, initial white blood counts, treatment and outcome

Case/Age (Yr)/Sex	Diagnosis	Treatment Stage	Initial Lymphocyte Cells/Mm^3	Initial Neutrophil Cells/Mm^3	Rx. ACV	Outcome
X/5/F	All	M	400	2300	IV	R
2Y/12/M	Aml	M	900	1400	IV	R

M=Maintenance, R=Recovered, IV=Intravenous.

There were three outbreaks of varicella in the ward. The first occurred in February-March, second in June-August and the third in September-October. It was not possible to be sure which patient or mother brought in the virus. All patients with varicella or zoster or those with affected mothers were transferred to an isolation room in an adjacent ward. Affected mothers were asked to go home and another family member had to come in to care for the patient. These children were given prophylactic ACV. The affected patients were treated with intravenous ACV, appropriate antibiotics, blood and other supportive medications as necessary. Reverse barrier nursing was practised with strict hand washing. The patients had their own thermometer and sphygnomanometer and linen were isolated for washing. An attempt was made to get nurses and doctors who were immune (i.e. history of varicella) to care for them but this was not always possible especially at night when there was limited staffing. The Oncology ward was closed from 9th to 25th July due to the large number of patients and mothers developing varicella. Viral titres were checked from all patients in the ward (using Complement fixation test done by Virology laboratory in UKM). Nineteen patients were tested, of which only 2 had titres > 64. All the others had titres < 8. These patients were given prophylactic oral ACV (< 6 years - 200mg tds; > 6 years - 400mg tds). Of these patients, only 1 developed varicella after completing the course of ACV.

Discussion

Varicella is a life-threatening infection in immunocompromised children. Pneumonitis has been reported to develop in 28% [3] of untreated cases with a mortality rate of 25% [3]. Pneumonitis is more likely to develop if the lymphocyte count is < 500/mm^3 and mortality increased if lymphocyte count is < 300/mm^3. Pneumonitis is also more likely to occur in haematological malignancy than in solid malignancy [3]. All the cases in this review were patients with haematological malignancy and the two patients who died had severe pneumonitis. The absolute lymphocyte count for the two patients who died were 0 and 700/mm^3. Although patient no. 9 had a lymphocyte count of 500/mm^3 and survived, he required ventilaton and was brain damaged after convalescence.

ACV has been shown in many studies to be effective in the treatment of varicella-zoster infection in immunocompromised patients [1,2,5]. Treatment should be instituted as early as possible in the course of infection to prevent visceral dissemination. It also alters the pattern of evolution of rash ie. new lesions are less likely to pustulate but heal directly from papules with or without crust formation and complete healing is faster. The period of fever and pain is also shortened. The main possible side-effects are renal insufficiency, reversible neurological reaction usually consisting of tremor and tissue inflammation if drug is extravasated. No side effects were noted in the patients above.

Although ACV is an extremely well tolerated drug with few associated side-effects in treatment of established varicella-zoster, prevention of primary infection should be looked into. We used ACV for prophylaxis in exposed susceptible patients. This was based on the good results of ACV used on bone marrow transplant recipients [6,7]. These transplant patients were given prophylaxis with ACV and they had significantly fewer episodes of herpes simplex virus and varicella zoster virus infection. Passive immunisation with Varicella-Zoster Immune Globulin (VZIG) had been reported to prevent or modify the course of varicella if given within 72 hours of exposure [8], but in newer studies [3], VZIG was shown not to decrease attack rates of those exposed but it reduced the severity of the disease and reduced the incidence of varicella pneumonitis to 11% ie. 50% reduction if compared to untreated patients. Presently this is not available in this country.

Active immunisation by live attenuated varicella virus would be a major goal in preventing this infection in immunocompromised children [10,11,12,13]. The initial fear was:

1. administering a live virus even though attenuated to an immunocompromised child.
2. fear of herpes zoster since this is a herpes virus and can produce latent infection.

Studies [9,10,11,12,13] have been done using live virus that has been attenuated by multiple passage in guinea pig and human tissue culture cells. The vaccine was first given to healthy children and then to immunocompromised children. These immunocompromised children vaccinated were in remission for 1 year (maintenance withheld for 1 week before and 1 week after vaccination for first dose). It conferred a protective level of about 80-85% after 1 dose and more than 90% after 2 doses[13], given 3 months apart. (Conversion rate was 95% in healthy children after 1 dose[13]). Only about 5% developed mild to moderate rash and there was a risk (10%)[12] of transmission of virus to others in the first month after vaccination. Transmission only occurred if the vaccinee developed the rash and these children had higher antibody titres than those without the rash. Hence vaccinees were not allowed to meet with children still on active treatment. The attack rate of clinical varicella in these vaccinees was 18%[12], which is much lower compared to attack rate of 80-90% of susceptible person with household exposure and the cases of clinical illness were mild (not given VZIG or ACV). There was no increase risk of relapse of leukaemia or zoster in the vaccinees. In fact, one study[14] showed that herpes zoster occurred more frequently in children with natural varicella than vaccinated leukaemic children. The duration of protection in healthy children was 97% up to 10 years after vaccination in studies done in Japan [13]. In immunocompromised children, there were indications of waning immunity during the second year after vaccination and hence to continue to give these children protection, it has been proposed to give them booster doses yearly without stopping chemotherapy.

In conclusion, this review highlights the severity of varicella in children with malignancy and the problem of outbreaks in an oncology ward. There is need to educate parents of these children about the consequence of this infection. Health care personnel and the parents must have a high suspicion of this infection whenever the child develops a vesicular rash especially if there has been exposure. Exposed susceptible children should be given ACV prophylaxis orally for one week as no VZIG is available and observed carefully. Children whose chemotherapy has been stopped completely and not received any immunosuppressive therapy for > 30 days do not require passive immunisation or antiviral therapy. In view of the effectiveness of varicella vaccination from all the studies done by various groups, it appears that immunisation against varicella would deserve serious consideration in the immunosuppressed children.

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