ORIGINAL ARTICLE

Peripheral Neuropathy in Patients with Acute Leukemia Treated with Vincristine

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ABSTRACT Between December 1993 and December 1994, 46 patients with acute leukemia treated with vincristine were evaluated for the possibilities of peripheral neuropathy. Of the 46 patients, 39 patients had acute lymphoblastic leukemia, and 7 had acute non-lymphoblastic leukemia. All patients had received vincristine; 29 (63%) of the 46 patients had it for 5 - 9 weeks, and 17 (37%) had it for 4 weeks or less. In 10 (21.7%) patients peripheral neuropathy was detected clinically, and in 35 patients (76%) the neuropathy was detected by electrodiagnostic examination. No evidence of neuropathy was detected in 11 patients. The electrodiagnostic examination was more sensitive than the clinical examination. Peripheral neuropathy, either detected clinically or by means of electromyography, occurred mostly in patients with the dosage of vincristine of 5-20 mg, and the duration of treatment of 5-9 weeks. **[Paediatr Indones 1995; 35:101-109]**

Introduction

The principles of treatment for acute leukemia are the combination of weekly intravenous vincristine and daily oral prednisone. Some centers add a third agent, such as L- asparaginase or daunorubicin. For central nervous system (CNS) leukemia prophylaxis most centers use intrathecal methotrexate or cytosine arabinoside.[1] Vincristine is a relatively common cause of peripheral neuropathy in children with malignancy, and the type of neuropathy is axonal degeneration.[2]

Selawry et al. reported that 87.5% of their cases suffered from peripheral

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neuropathy.[3] The diagnosis of peripheral neuropathy can be established by clinical signs and symptoms, or by eletrodiagnostic tool, i.e., electromyography (EMG); but usually in 60% of them the clinical signs and symptoms were normal.[4] Electromyographic examination is the most sensitive test to make an early diagnosis of peripheral neuropathy.

The neurological side effects of L-asparaginase is encephalopathy with the neurological signs and symptoms consist of lethargy, somnolence, confusion, and sometimes convulsion and neurological deficit. The neurological signs and symptoms are not peripheral but of the central type.[5] Methotrexate is given intrathecally, and the neurological side effects are leukoencephalopathy, and paraplegia as a local sign of side effect. Sometimes the patients suffered from aseptic meningitis and cerebral calcification.[6,8] Cytosine arabinoside sometimes is given intrathecally, and the toxic effects are on cerebellar area with the signs and symptoms consist of ataxia, dysarthria, dysdiadochokinesis and dysmetria. The local signs is paraplegia.

From the above data it can be concluded that peripheral neuropathy in patients with acute leukemia treated with cytostatic drugs was caused by vincristine.

The aim of the present study is to describe the occurrence of peripheral neuropathy in pediatric patients with acute leukemia treated with cytostatic drugs especially vincristine, and the apparent relation between the duration of treatment, the total dosage of vincristine, and the occurrence of clinical and laboratory detected peripheral neuropathy.

Methods

This study was a cross sectional descriptive study on patients with acute leukemia. The study subjects consisted of 46 leukemic patients hospitalized at the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta, between December 1993 and December 1994.

All patients were examined clinically and electromyographically to detect the occurrence of peripheral neuropathy. The results of the clinical examination were compared with the results of the electromyographic examination. Evaluation was also performed to detect the possible relation between the duration of treatment, the dosage of vincristine and the occurrence of peripheral neuropathy.

Results

Between December 1993 and December 1994, forty six patients with acute leukemia were evaluated for the possibility of peripheral neuropathy. They consisted of 39 patients with acute lymphoblastic leukemia, and 7 patients with acute non-lymphoblastic leukemia. The youngest patient was 11 months, and the oldest was 15 years. The age distribution of the patients is depicted in Table 1.

The nutritional states of the 46 patients can be seen in Table 2. Twenty of the 46 patients were well-nourished, 16 patients were undernourished, and 10 were severely malnourished.

The cytostatic drugs that were used to treat the patients were vincristine in all patients, L-asparaginase in 31 patients, methotrexate in 28 patients, cytosine arabinoside in 28 patients, and adriamycine in 19 patients (Table 3).

Table 1. Age distribution of the patients

Age (years)	No	%
0 - 4	17	36.9
5 - 9	15	32.6
10 - 15	14	30.5
Total	46	100.0

Table 2. The nutritional states of the patients

Nutritional states	No	%
Well-nourished	20	43.5
Undernourished	16	34.8
Severely malnourished	10	21.7
Total	46	100.0

Table 3. Cytostatic drugs used in this series

Drugs	No. of patients	%
Vincristine	46	100.0
L-asparaginase	31	67.4
Methotrexate	28	60.8
Cytosine arabinoside	28	60.8
Adriamycine	19	41.3

The duration of treatment was between 1 and 9 weeks. Eight (17.4%) of the 46 patients were treated for less than 3 weeks, 9 patients (19.6%) for 3-4 weeks, and 29 patients (63%) for 5-9 weeks (Table 4).

Table 4. Duration of vincristine treatment

Duration of treatment	No. of cases	%
< 3 weeks	8	17.4
3 - 4 weeks	9	19.6
5 - 9 weeks	29	63.0
Total	46	100.0

Table 5 shows the results of clinical and laboratory examinations. By clinical examination only 10 (21.7%) of the 46 patients were judged to have peripheral neuropathy, while by using laboratory examination 35 (76%) of the 46 patients were diagnosed of having peripheral neuropathy.

Table 5. Results of clinical and laboratory examinations

Results	No	%
Clinical neuropathy	10	21.7
Laboratory neuropathy	35	76

Patients with clinical neuropathy were called as symptomatic neuropathy, and patients with laboratory neuropathy but without symptoms were called as asymptomatic neuropathy. Table 6 shows that symptomatic neuropathy was found in 10 patients (21.7%), and asymptomatic neuropathy in 25 patients (54.4%). In 11 (23.9%) patients no neuropathy was detected.

Table 7 shows the sex distribution of patients with peripheral neuropathy. Six (20.7%) of the 10 patients with symptomatic neuropathy were males. Sixteen

(55.2%) of the 25 patients with asymptomatic neuropathy were males, and 9 (53%) were females.

Table 6. Types of neuropathy

Types of neuropathy	No	%
Symptomatic	10	21.7
Asymptomatic	25	54.4
Normal	11	23.9
Total	46	100.0

Table 7. Distribution of neuropathy according to sex

Neuropathy	Males	Females	Total
Symptomatic	6 (20.7%)	4 (23.5%)	10 (21.7%)
Asymptomatic	16 (55.2%)	9 (53.0%)	25 (54.4%)
Normal	7 (24.1%)	4 (23.5%)	11 (23.9%)
Total	29 (100%)	17 (100%)	46 (100%)

The distribution of peripheral neuropathy according to age group of patients can be seen in Table 8. Of 17 patients aged 0-4 years, two (11.8%) of them suffered from symptomatic neuropathy, 8 patients (47%) suffered from asymptomatic neuropathy, and 7 (41.2%) were normal. There were 15 patients with the age group of 5-9 years; six (40%) of them suffered from symptomatic neuropathy, 8 patients (53.3%) suffered from asymptomatic neuropathy, and 1 (6.7%) was normal. Out of 14 patients with the age group of 10-15 years two (14.3%) suffered from symptomatic neuropathy, 9 (64.3%) had asymptomatic neuropathy, and 3 patients (21.4%) were normal.

Table 8. Distribution of peripheral neuropathy according to age groups of patients with acute leukemia

Neuropathy	Age groups (years)			Total
	(0-4)	(5-9)	(10-15)	
Symptomatic	2 (11.8%)	6 (40%)	2 (14.3%)	10 (21.7%)
Asymptomatic	8 (47%)	8 (53.3%)	9 (64.3%)	25 (54.4%)
Normal	7 (41.2%)	1 (6.7%)	3 (21.4%)	11 (23.9%)
Total	17 (100%)	15 (100%)	14 (100%)	46 (100%)

Table 9 shows the relationship between the peripheral neuropathy and the nutritional states of patients with acute leukemia. The number of patients with good nutritional states was 20, three (15%) of them had symptomatic neuropathy, 10 (50%) patients had asymptomatic neuropathy, and 7 (35%) patients were normal. The number of patients with undernutrition was 16, six (37.5%) of them suffered from symptomatic neuropathy, 9 patients (56.3%) had asymptomatic neuropathy, and 1 patient was normal. Out of 10 patients with poor nutritional states, one (10%) of them suffered from symptomatic neuropathy, 6 patients (60%) suffered from asymptomatic neuropathy, and 3 patients (30%) were normal.

Table 10 shows distribution of peripheral neuropathy and the dosage of vincristine. There were 20 patients receiving 0-4 mg of vincristine; one (5%) of them had symptomatic neuropathy, 8 (40%) patients had asymptomatic neuropathy, and 11 (55%) patients were normal. Out of 26 patients who had received 5-20 mg

of vincristine, nine (34.6%) had symptomatic neuropathy, and 17 patients (65.4%) had asymptomatic neuropathy.

Table 9. Distribution of peripheral neuropathy according to the nutritional states of patients

Neuropathy	Nutritional states			Total
	Good	Undernutrition	Poor	
Symptomatic	3 (15%)	6 (37.5%)	1 (10%)	10 (21.7%)
Asymptomatic	10 (50%)	9 (56.3%)	6 (60%)	25 (54.4%)
Normal	7 (35%)	1 (6.2%)	3 (30%)	11 (23.9%)
Total	20 (100%)	16 (100%)	10 (100%)	46 (100%)

Table 10. Distribution of peripheral neuropathy and the dosage of vincristine

Neuropathy	Dosage of vincristine (mg)		Total
	(0-4)	(5-20)	
Symptomatic	1 (5%)	9 (34.6%)	10 (21.7%)
Asymptomatic	8 (40%)	17 (65.4%)	25 (23.9%)
Normal	11 (55%)	0	11 (23.9%)
Total	20 (100%)	26 (100%)	46 (100%)

Table 11 shows the apparent relationship between the peripheral neuropathy and the duration of treatment with cytostatic drugs in patients with acute leukemia. There were 8 patients who were had been treated for less than 3 weeks; none of them suffered from neuropathy. Out of 9 patients who had been treated for 3-4 weeks, none suffered from symptomatic neuropathy, 6 patients suffered from asymptomatic neuropathy, and 3 patients were normal. Out of 29 patients who had been treated for 5-9 weeks, ten patients (34.5%) suffered from symptomatic neuropathy, 19 patients (65.5%) suffered from asymptomatic neuropathy, and none was normal.

Table 11. Distribution of peripheral neuropathy according to the duration of cytostatic treatment

Neuropathy	Duration of treatment (weeks)			Total
	(<3)	(3-4)	(5-9)	
Symptomatic	0 (0%)	0 (0%)	10 (34.5%)	10 (21.7%)
Asymptomatic	0 (0%)	6 (66.6%)	19 (65.5%)	25 (54.4%)
Normal	8 (100%)	3 (33.4%)	0 (0%)	11 (23.9%)
Total	8 (100%)	9 (100%)	29 (100%)	46 (100%)

Table 12 shows the distribution of patients with peripheral neuropathy according to the age and the total dose of vincristine. Of the 17 patients with the age group of 0-4 years, 16 had received 0-4 mg of vincristine, and only one patient had 5-20 mg of vincristine. Nine (56.3%) of the 16 patients who had received 0-4 mg of vincristine suffered from peripheral neuropathy, and one patients with vincristine 5-20 mg also suffered from peripheral neuropathy.

The number of patients aged 5-9 years was 15, three of them had received 0-4 mg of vincristine, and 12 patients had received 5-20 mg of vincristine. Two of the 3 patients who had received 0-4 mg of vincristine suffered from peripheral neuropathy, and all 12 patients who had received 5-20 mg of vincristine suffered from peripheral neuropathy (5 of them had symptomatic, and 7 had asymptomatic neuropathy).

The number of patients with the age group of 10-15 years was 14, three of them had received 0-4 mg of vincristine, and 11 had 5-20 mg of vincristine. None of the 3 patients who had received 0-4 mg of vincristine suffered from peripheral neuropathy, and all the 11 patients who had received 5-20 mg of vincristine suffered from peripheral neuropathy (two of them had symptomatic and 9 had asymptomatic neuropathy).

Table 13 shows the distribution of peripheral neuropathy according to the nutritional states and the total dosage of vincristine. The number of patients with good nutritional states was 20, fourteen of them had received 0-4 mg of vincristine, and 6 patients had 5-20 mg of vincristine. Seven (50%) of the 14 patients who had received 0-4 mg of vincristine suffered from peripheral neuropathy, and all 6 patients who had received 5-20 mg of vincristine suffered from peripheral neuropathy.

There were 16 patients who were undernourished; five of them had received 0-4 mg of vincristine, and 11 of them had 5-20 mg of vincristine. Four (80%) of the 5 patients with vincristine 0-4 mg suffered from peripheral neuropathy, and all the 11 patients with vincristine 5-20 mg suffered from neuropathy.

Three out of 10 patients with poor nutritional states had received 0-4 mg of vincristine, and 7 of them had 5-20 mg. None of the three patients who had received 0-4 mg of vincristine suffered from peripheral neuropathy, and all patients who had received 5-20 mg of vincristine suffered from peripheral neuropathy, 1 patient was symptomatic and 6 patients were asymptomatic.

Table 12. Distribution peripheral neuropathy according to age groups and the total dosage of vincristine

Neuropathy	Age groups (years)						Total
	0 - 4		5 - 9		10 - 15		
	Dosage of vincristine (mg)						
	(0-4)	(5-20)	(0-4)	(5-20)	(0-4)	(5-20)	
Symptomatic	2	0	1	5	0	2	10
Asymptomatic	7	1	1	7	0	9	25
Normal	7	0	1	0	3	0	11
Total	16	1	3	12	3	11	46

Table 14 shows the distribution of peripheral neuropathy according to the duration of treatment and the total dosage of vincristine. The number of patients with the duration of treatment of less than 3 weeks were 8, three to four weeks were 9, and 5-9 weeks were 29. All the 8 patients treated with vincristine for less than 3 weeks had received 0-4 mg of vincristine, and none of them suffered from peripheral neuropathy. There were 9 patients with the duration of treatment of 3-4 weeks; seven of them had received 0-4 mg of vincristine, and 4 (57.1%) of the 7 patients suffered from peripheral neuropathy, while all the 2 patients with vincristine 5-20 mg suffered from peripheral neuropathy. There were 29 patients who had been treated for 5-9 weeks, seven patients had received 0-4 mg of vincristine, twenty two patients had 5-20 of vincristine, and all the 29 patients suffered from peripheral neuropathy.

Table 13. Distribution of peripheral neuropathy according to nutritional states and total dosage of vincristine

Neuropathy	Nutritional states						Total
	Good		Undernutrition		Poor		
	Dosage of vincristine (mg)						
	(0-4)	(5-20)	(0-4)	(5-20)	(0-4)	(5-20)	
Symptomatic	2	1	1	5	0	1	10
Asymptomatic	5	5	3	6	0	6	25
Normal	7	0	1	0	3	0	11
Total	14	6	5	11	3	7	46

Discussion

Table 1 shows that the age of the patients was evenly distributed among the groups. This finding is different with other studies which show that usually in acute lymphoblastic leukemia the peak age incidence is 3-4 years, and in acute non-lymphoblastic leukemia is about the same frequency at all ages of childhood.[8]

Table 14. Distribution of peripheral neuropathy according to the duration and total dosage of vincristine treatment

Neuropathy	Duratation of treatment (weeks)						Total
	< 3		3 - 4		5 - 9		
	Dosage of vincristine (mg)						
	(0-4)	(5-20)	(0-4)	5-20)	(0-4)	5-20)	
Symptomatic	0	0	0	0	3	7	10
Asymptomatic	0	0	4	2	4	15	25
Normal	8	0	3	0	0	0	11
Total	8	0	7	2	7	22	46

The nutritional status of the 46 patients was good in 20 patients (43.5%), undernutrition in 16 patients (34.8%), and poor in 10 patients (21.7%) (Table 2). The large percentage (56.5%) of patients, therefore, suffered from undernutrition or malnutrition; these conditions might be due to the disease itself.

All the 46 patients had received vincristine; other drugs received were L-asparaginase, methotrexate, cytosine arabinoside and adriamycine. Peripheral neuropathy usually is caused by vincristine;[2] other drugs usually cause abnormalities of cerebrum or cerebellum.

Twenty nine (63%) of the 46 patients had received vincristine for 5-9 weeks (Table 4). Some studies reported that longer duration of treatment with cytostatic drugs will increase the possibility of the occurrence of peripheral neuropathy;[3,5] These 29 patients had the higher risk the occurrence of peripheral neuropathy.

Table 5 depicts that laboratory examination, i.e,. electromyography, by mea-

suring nerve conduction velocity and amplitude, was more sensitive than the clinical examination in detecting peripheral neuropathy. By electromyography peripheral neuropathy could be detected in 35 patients (76%), and by clinical evaluation only in 10 patients (21.7%). By electromyography the occurrence of peripheral neuropathy could be detected earlier, so that severe peripheral neuropathy could be prevented.

Peripheral neuropathy with clinical signs and symptoms was called symptomatic neuropathy, and that without clinical signs and symptoms was called asymptomatic neuropathy; the diagnosis of asymptomatic neuropathy was based on the abnormalities of the EMG. In this study the number of patients with symptomatic neuropathy was 10 (21.7%) and that with asymptomatic neuropathy was 25 (54.4%) (Table 6). These figures are lower if compared with other study;[3] which found 40% symptomatic neuropathy and 87.5% asymptomatic neuropathy. This difference might be due to the duration of treatment; in this study most of the patients had received vincristine for four weeks or less, while in other study for 2 months or more.[3] The longer duration of treatment will increase the possibility the occurrence of peripheral neuropathy.[3,5]

From Table 8 can be seen that patients with the age group of 5-9 years suffered from peripheral neuropathy more than the other groups. In 5-9 years age group, 14 (93.3%) of the 15 patients suffered from neuropathy, while in the group of 0-4 years and 10-15 years were 58.8% and 78.6%, respectively. Actually this condition was not due to the age groups, but related to the dosage of vincristine. The number of patients with the age group of 0-4 years was 17, and 16 of them had received 0-4 of vincristine, only one patient had received 5-20 mg of vincristine, while out of 15 patients with the age group of 5-9 years and 12 (80%) of them had received 5-20 mg of vincristine (Table 12). It can be concluded that the peripheral neuropathy was related to the dosage of vincristine.

Table 9 shows that patients with undernutrition suffered from peripheral neuropathy more than the other groups. There were 16 patients, and 15 (93.3%) of them suffered from peripheral neuropathy, while in patients with good nutritional states only 13 (65%) out of 20 suffered from peripheral neuropathy, and 7 out of 10 patients with poor nutritional states suffered from peripheral neuropathy. These data suggest that peripheral neuropathy was not related to nutritional states but to the dosage of vincristine (Table 13). Had the peripheral neuropathy related to nutritional states, than patients with poor nutritional states should have been suffered from peripheral neuropathy more than the other groups.

In Table 10 we can see that all 26 patients who had received 5-20 mg of vincristine suffered from peripheral neuropathy, while out of 20 patients who had received 0-4 mg vincristine only 9 (45%) suffered from peripheral neuropathy. Furthermore, Table 11 shows that all 29 patients who had received 5-9 weeks of vincristine treatment suffered from peripheral neuropathy, while out of 17 patients who had received vincristine for 4 weeks or less only 6 patients (31.8%) suffered from peripheral neuropathy. It means that the high dosage and the longer duration of treatment with vincristine will increase the possibility of the occurrence of the peripheral neuropathy (Table 14). These findings are not different with other studies.[5,9]

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