Original Article

JHSMR Journal of Health Science and Medical Research

Vincristine and Peripheral Neuropathy in Acute Lymphoblastic Leukemia Children

Tipaporn Thongmak, M.D., Najwa Yuthasompop, M.D.

Pediatric Division, Hatyai Hospital, Hat Yai, Songkhla 90112, Thailand.

Received 29 May 2023 ● Revised 23 June 2023 ● Accepted 27 June 2023 ● Published online 18 September 2023

Abstract:

Objective: Peripheral neuropathy is a common neurological side effect in acute lymphoblastic leukemia (ALL) pediatric patients, receiving vincristine treatment. This study aims to explore the frequency, clinical, and electrodiagnosis of peripheral neuropathy of ALL patients.

Material and Methods: This study was a retrospective cohort study, using medical record reviews of children who, diagnosed and undergoing treatment for acute lymphoblastic leukemia, from 1st January 2018 till 31st December 2022.

Results: One hundred and ninety-seven patients were diagnosed with ALL and received chemotherapy. Ten patients had clinical and electrodiagnostic studies of peripheral neuropathy. B-cell type and high- risk classification were the most common in these patients. The most common symptom was bilateral foot drop and all patients had hyporeflexia. The mean cumulative dose of vincristine was 13.35±2.12 mg/m^2. The axonal neuropathy, with motor dominantly and the peroneal nerves, were the highest abnormal finding in electrodiagnosis testing.

Conclusion: This report addresses the frequent and clinical of patients with peripheral neuropathy. Foot drop and hyporeflexia might be helpful in early detection of peripheral neuropathy in ALL patients.

Keywords: acute lymphoblastic leukemia, peripheral neuropathy, vincristine

Contact: Tipaporn Thongmak, M.D.
Pediatric Division, Hatyai Hospital, Hat Yai, Songkhla 90112, Thailand.
E-mail: tipaing@gmail.com

J Health Sci Med Res 2024;42(2):e2023989
doi: 10.31584/jhsmr.2023989
www.jhsmr.org

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cause of cancer in children within Thailand. Incidence from 1990 to 2011, was 36.1 cases per million person-years[1]. The 5-year-survival rate outcome increased from 38.3% to 52.3% from 1990 to 2000, and 2001 to 2011, respectively[2]. Chemotherapy is the main treatment of ALL; however, one of the serious non-hematologic side effects is peripheral neuropathy, which leads to impairing the patient's quality of life. Chemotherapy agents usually associated with peripheral neuropathy consist of: platinum drugs, vinca alkaloid, Taxanes and Thalidomide[3]. Thai-POG protocol, which is the national protocol for the treatment of childhood cancer, is applied for treatment for ALL children in Thailand. The treatment of ALL in Thai-POG protocol provides for 2.5 to 3 years; and comprises of: Prednisolone, Vincristine, L-Asparaginase, Methrotrexante, Mercaptopurine, Doxorubicin, Cyclophosphamide, Cytarabine, and Thioguanine. Vincristine is a vinca alkaloid agent and is used in many phases of the Thai-POG protocol; such as in the induction, consolidation, intensification, and maintenance phases. Vincristine inhibits the synthesis of spindle microtubules during cell division, which causes tumor cell necrosis. Additionally, it causes Wallerian degeneration of the neuron that affects axonal transportation, and consequently axonal neuropathy[4-7].

Many children having undergone chemotherapy treatment have experienced peripheral neuropathy. The prevalence of ALL with peripheral neuropathy in Malaysia was 15.8%[8] Its neurological manifestation is grouped into three functions; sensory, motor, and autonomic[9], and patients may have pain, paresthesia, tingling, weakness, cramps, constipation, diarrhea, and abnormal sweating[4,10]. Chemotherapy-induced peripheral neuropathy is diagnosed by abnormalities of history, physical examination, and nerve electrophysiology[1,4]. Peripheral neuropathy not only affects the patient's quality of life but also leads to decrease the vincristine dose, which could affect the overall survival of the patient[11].

The clinical of peripheral neuropathy in ALL children was evaluated throughout the chemotherapy treatment. This study aimed to explore the frequency, clinical, and electrodiagnostic results of peripheral neuropathy of ALL children that received chemotherapy.

Material and Methods

This retrospective cohort study reviewed the medical records of children diagnosed and treated for acute lymphoblastic leukemia; from 1st January 2018 until 31st December 2022.

Inclusion criteria

Children aged below 18 years old, who were diagnosed and treated for ALL, via the Thai-POG protocol; which is the national protocol for the treatment of childhood cancer in Hatyai Hospital Thailand.

Nerve electrodiagnosis confirming peripheral neuropathy, by physical medicine and rehabilitation physician[5].

Exclusion criteria

The children who had underlying diabetes mellitus, congenital peripheral neuropathy, Down syndrome, cerebral palsy, and CNS involvement of the ALL patients who presented with neuropathy.

Medical records having insufficient data to review

Peripheral neuropathy was assessed according to history taking and neurological examination during the sessions of chemotherapy. These included: history of pain, paresthesia, tingling, dizziness, weakness, cramps, constipation, diarrhea, and abnormal sweating. The neurological examination included: the cranial nerves (CN II-XII), pinprick, proprioception, joint positioning sense,

muscle strength and deep tendon reflexes (DTR). The gait assessment was conducted as well as, the toe and heel positions when walking when possible. The neurological examination was tailored and interpreted in the context of the patients' age.

Patients that had abnormal clinical and neurological examinations were referred for electrodiagnosis. Nerve electrodiagnosis was performed by physical medicine and rehabilitation physicians. The data included; onset latency, distal latency, conduction velocities, amplitude of the compound muscle action potential (CMAP), the peak latency and amplitude of sensory nerve action potential (SNAP) and F waves (if possible).

The following information was collected from age at diagnosis of peripheral neuropathy, gender, type, classification of ALL, symptoms, physical examination, the accumulated dose of vincristine, the pattern of peripheral neuropathy, completed blood count and liver function test at diagnosis and history of anti-fungal medication. A descriptive analysis was performed. Frequency, percentage, and means were calculated.

Results

In total there were 197 children diagnosed and who received chemotherapy for acute lymphoblastic leukemia: from between 1st January 2018 until 31st December 2022. Ten patients suffered from peripheral neuropathy during their chemotherapy treatment. There were 4 males (40%), mean age was 8.40±4.62 years old. Most of the patients were B-cell type and half had a high-risk classification. Bilateral feet drop was the most common complaint and all of them had hyporeflexia. The mean cumulative dose of vincristine was 13.35±2.12 mg/m^2 (range 6-25.5). Axonal neuropathy was the most common finding in electrodiagnosis. The initial laboratory test revealed, the mean white blood cell as 42,346 per mm^3 (range 1,460–289,840), the mean blast cell was 45.5% (range 0-97), the mean hemoglobin was 7.1 g/dl (range 2.4-11.3), and the mean platelet was 42,870 per mm^3 (range 1,700-100,000). The initial abnormal liver enzyme (AST, AST) was 20%.

The clinical characteristic of these patients is shown in Table 1.

A nerve conduction study was performed on a patient had clinical peripheral neuropathy. Table 2 presents the nerve conduction study parameters value, which consisted of distal latency, amplitude and conduction velocity on each nerve in patients who had ALL and peripheral neuropathy. Motor nerves were affected by neuropathy in ALL patients. All patients had decreased CMAPs amplitude of the peroneal nerves.

Discussion

The frequency of peripheral neuropathy in pediatric ALL patients in this study (5.07%) was lower than in previous study, with the India study being 13.8% of completed remission patient[12] and the Netherlands study having 82%[11]. The vincristine-induced peripheral neuropathy (VIPN) score; such as the pediatric modified total neuropathy score (ped-mTNS) was neither applied or reported in our this study due to the context of age in some patients[4]. The items of ped-mTNS are sensory symptoms, functional symptoms, autonomic symptoms and physical examination; such as light touch sensation, pin sensibility, vibration sensibility, muscle strength and deep tendon reflexes[12].

The VIPN score may aid in early diagnosis and evaluation of peripheral neuropathy. However, the most common symptoms were distal weakness (60%) and abnormality of deep tendon reflex (100%) that are similar to a previous study[4].

According to the morphology and risk classification, the results in this study were similar to the previous studies[13,14]. B-cell type immunophenotype and high-risk classification were 80% and 50%, respectively in study. The previous study in Indian children showed 74 percent

of B-cell type[13]. Another study form Mexico reported 93.8% of B-cell type and 59.4% of high-risk classification[14]. In regards to initial blood count at diagnosis of neuropathic patients, the result of this study is similar to the India study, in that the mean hemoglobin was 7.5 g/dl, the median white blood cell count was 6,200 per mm^3 and the median platelet count was 5,600 per mm^3 [13]. In addition, the cell type, risk classification, initial hemoglobin, white blood cell count, and platelet count were not associated with the risk factors of peripheral neuropathy[13].

The mean cumulated dose in this study was 13.35±2.12 mg/m^2, as in the Korean study wherein, the mean cumulative dose was 14.99±1.21 mg/m^2 [2, 7] based on these data, it is important in clinical practice that doctors closely monitor symptoms and signs; such as foot drop, numbness and hyporeflexia, when the patients receive vincristine at the cumulative dose range 13-15 mg/m^2, for early diagnosis of peripheral neuropathy.

The nerve electrodiagnosis study showed a higher rate of motor nerve involvement than sensory nerve involvement in both this study and previous studies[7,13]. The nerve conduction study reports showed more reduction in the amplitude of the motor nerve than the sensory nerve, which inferred to the motor nerves were damaged more severely. The axon-type of neuropathy was the most common type of chemotherapy-induced neuropathy in both this study and previous studies[4,7,13]. The peroneal nerve was the most frequent abnormality in this study, which was the same as the previous studies[4,7,13].

Table 1 Patient clinical characteristic

No	Age (years)	Gender	Type and classification	Clinical and physical examination	Cumulative vincristine dose at diagnosis	Type of neuropathy	Initial WBC	Initial Blast (%)	Initial Albumin	Abnormal liver enzyme at initial
1	12	Female	B-cell, high risk	Bilateral foot drop and DTR 0	10.5	Axonal neuropathy of motor	34,030	68	4.52	No
2	13	Male	T-cell, high risk	Bilateral foot drop and DTR 0	6	Axonal and demyelination neuropathy of motor and sensory	1,460	0	3.34	Yes
3	5	Female	B-cell, high risk	No clinical but DTR 0	25.5	Axonal neuropathy of motor and sensory	289,840	97	4.1	No
4	10	Female	B-cell, high risk	No clinical but DTR 0	24	Axonal neuropathy of motor	1,580	28	3.6	No
5	6	Male	B-cell, standard risk	No clinical but DTR 0	22.5	Axonal neuropathy of motor and sensory	7,110	25	3.2	Yes
6	3	Female	B-cell, standard risk	Bilateral foot drop and DTR 0	7.5	Axonal neuropathy of motor	8,040	77	3.87	No
7	6	Female	B-cell, standard risk	Bilateral drop and DTR 0	9	Axonal neuropathy of motor	8,690	36	3.17	No
8	17	Male	T-cell, very high risk	Numbness and DTR 0	10.5	Axonal neuropathy motor and sensory	21,230	30	3.76	No
9	3	Male	B-cell, standard risk	Bilateral foot drop and DTR 0	10.5	Axonal neuropathy of motor	4,800	0	3.7	No
10	9	Female	B-cell, high risk	Constipation, bilateral foot drop, DTR 0	7.5	Axonal neuropathy of motor	46,680	94	3.25	Yes

WBC=white blood cell, DTR=deep tendon reflex

Table 2 Nerve conduction study characteristics

Nerve	Motor			Nerve	Sensory		
	Latency (ms)	Amplitude (mV)	NCV (m/s)		Latency (ms)	Amplitude (CV)	NCV (m/s)
Median				**Median**			
Means±S.D.	3.92 ±1.15	3.51±2.0	51.86±7.45	Means±S.D.	2.89±0.55	14.87±7.68	52±7.78
(Max, Min)	(5.94, 2.45)	(6.2, 0.3)	(62, 41)	(Max, Min)	(3.59, 2.14)	(25.2, 3.45)	(61,36)
Ulnar				Ulnar			
Means±S.D.	2.59±0.38	4.21±2.28	57.44±6.02	Means±S.D.	2.37±0.47	16.82±13.56	53.11±8.66
(Max, Min)	(3.13, 2.03)	(9.3, 1.1)	(67, 50)	(Max, Min)	(3.23, 1.72)	(46.6, 3.18)	(66, 40)
Peroneal				Sural			
Means±S.D.	4.09±2.05	0.63±0.57	48±11.19	Mean±S.D.	3.74±3.29	8.17±5.55	54.5±21.50
(Max, Min)	(6.98, NR)	(1.8, NR)	(69, NR)	(Max, Min)	(11.77, 1.61)	(19.10, 2.03)	(87,14)
Tibial							
Means±S.D.	3.27±0.67	7.14±4.14	43±3.43				
(Max, Min)	(4.27, 2.29)	(13.8, 1.6)	(48, 37)				

NCV=Nerve conduction velocity, CV=conduction velocity, m/s=meter/second, mV=microvoltage, ms=millisecond, S.D.=standard deviation

Table 3 Findings of number of patients having abnormal nerve conduction study

Nerve tested (N=10)	Prolonged distal latency N (%)	Decreased amplitude N (%)	Decreased nerve conduction velocity N (%)
Median (motor)	1 (10%)	6 (60%)	2 (20%)
Ulnar (motor)	0	6 (60%)	0
Peroneal (motor)	2 (20%)	10 (100%)	1(10%)
Tibial (motor)	0	2 (20%)	0
Median (sensory)	1 (10%)	2 (20%)	0
Ulnar (sensory)	1 (10%)	1 (20%)	0
Sural (sensory)	1 (10%)	1 (10%)	0

Limitations

This study was a case series that initially reported on the non-hematological side effects of chemotherapy, especially vincristine. This study contained a limited number of patients, was pragmatic in its approach and conducted over a short duration; hence, further plans are to collect more data, to apply the VIPN score and to follow up on the clinical recovery of the patients.

Conclusion

Vincristine and peripheral neuropathy in children with ALL were mostly diagnosed by neurological examination, especially deep tendon reflexes. The nerve electrodiagnosis reported the most common type as axonal neuropathy, with motor dominance. The cumulative dose was 13.35 mg/m^2, which might be helpful for the physician to closely monitor the clinical early signs for nerve electrodiagnosis.

Ethics approval of research

This case report received a clearance from the ethics committees of Hatyai Hospital (HHY EC 076-65-01).

Conflict of interest

There are no conflicts of interest to declare.

References

1. England JD, Gronseth GS, Franklin G, Miller RG, Asbury AK, Carter GT, et al. Distal symmetric polyneuropathy: a definition for clinical research: report of the american academy of neurology, the american association of electrodiagnostic medicine, and the american academy of physical medicine and rehabilitation. Neurology 2005;64:199–207.
2. Peterson CC, Demanelis K, Rentschler K, Meza R, Sriplung H, Wiangnon S, et al. Childhood cancer incidence and survival in Thailand: A comprehensive population-based registry analysis, 1990–2011. Pediatr Blood Cancer 2019;66:e27428. doi: 10.1002/pbc.27428
3. Argyriou AA, Bruna J, Marmiroli P, Cavaletti G. Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. Crit Rev Oncol Hematol 2012;82:51-77.
4. Kava M, Walsh P, Srinivas Jois R, Cole C, Lewis B, Nagarajan L. Clinical and electrophysiological characteristics of vincristine induced peripheral neuropathy in children during cancer chemotherapy: does vitamin e have a role. JICNA 2017;17;75. doi: 10.17724/jicna.2017.75
5. Beijers AJ, Jongen JL, Vreugdenhil G. Chemotherapy-induced neurotoxicity: the value of neuroprotective strategies. Neth J Med 2012;70:18-25.
6. Custodio C. Electrodiagnosis in cancer rehabilitation. Phys Med Rehabil Clin N Am 2017;28:193-203.
7. Jeong JG, Ahn CH, Min YS, Kim SE, Kim JY, Jung TD. Electrophysiologic pattern s of symptomatic vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia. J Clin Med 2023;12:686. doi: 10.3390/jcm12020686
8. Tay C, Lee V, Ong L, Goh K, Ariffin H, Fong C. Vincristine-induced peripheral neuropathy in survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2017;64:10.1002/pbc.26471. doi: 10.1002/pbc.26471
9. Gilchrist L. Chemotherapy-induced peripheral neuropathy in pediatric cancer patients. Semin Pediatr Neurol 2012;19:9-17.
10. Hausheer FH, Schilsky RL, Bain S, Berghorn EJ, Lieberman F. Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy. Semin Oncol 2006;33:15-49.
11. van de Velde ME, van den Berg MH, Kaspers GJL, Abbink FCH, Twisk JWR, van der Sluis IM, et al. The association between vincristine-induced peripheral neuropathy and health-related quality of life in children with cancer. Cancer Med 2021;10:8172-81.
12. Özdemir B, Gerçeker GO, Özdemir EZ, Yıldırım BG, Ören H, Yiş U et al. Examination of the psychometric properties of pediatric-modified total neuropathy score in turkish children with cancer. J Pediatr Nurs 2023;69:31-7.
13. Jain P, Gulati S, Seth R, Bakhshi S, Toteja G, Pandey R. Vincristine-induce neuropathy in childhood all (acute lymphoblastic leukemia) survivors: prevalence and electrophysiological characteristics. J Child Neurol 2014;29:932-7.
14. Vivas-Rosales IJ, Garcia-Saaverdra L, Martin-Trejo JA, Mejia-Arangure JM, Victorio-Garcia NP, Herrera-Landero A, et.al. Chemotherapy-induced peripheral neuropathy is a subpopulation mexican pediatric patients with acute lymphoblastic leukemia. Iran J Pediatr 2017;27:e11844. doi: 10.5812/ijp.11844.