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ORIGINAL ARTICLE

Clinical and Electrophysiological Characteristics of Vincristine Induced Peripheral Neuropathy in Children during Cancer Chemotherapy: Does Vitamin E have a role.

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ABSTRACT

Background: Vincristine is a chemotherapeutic agent frequently used in the treatment of childhood cancer. Peripheral neuropathy is an important side effect of Vincristine. We assessed the frequency, severity and type of peripheral neuropathy in children on Vincristine using clinical parameters and nerve conduction studies. As the role of Vitamin E in chemotherapy induced neuropathy is unclear, we explored Vitamin E levels prior to and during therapy.

Methods: Children with cancer treated with Vincristine were enrolled. Symptoms and signs of motor, sensory and autonomic peripheral neuropathy at baseline and at 3, 6 and 12 month follow up were documented. A modified total neuropathy score grading was undertaken. Nerve conduction studies (NCS) were undertaken and vitamin E levels measured at the time of these assessments.

Results: 28 children (19 girls, 9 boys), ranging in age from 0.5 – 15.5 years (mean: 6.2 years and median age -5 years) completed the study. Acute lymphoblastic leukaemia was the commonest diagnosis in 19 children, followed by brain tumours in 4, Wilm's tumour in 3 and one each of rhabdomyosarcoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma and Langerhans cell histiocytosis. Twenty seven received Vincristine (21 for >12 months, 7 for 6 months only), one had vinblastine.

None of the patients had evidence of peripheral neuropathy at enrolment. 93 % had evidence of neuropathy clinically and/or electrophysiologically. Weakness, pain and constipation were the most common symptoms and the most common sign was loss of ankle reflexes. The peripheral neuropathy was mild in most cases. Plasma levels of vitamin E remained in the normal range; however there was a significant drop from the baseline value.

Conclusions: Mild motor-sensory peripheral neuropathy assessed clinically and electrophysiologically, occurs in the majority of children on Vincristine treatment. The statistically significant drop in average vitamin E levels during treatment is unlikely to be of clinical significance as the values remained in the normal range.

Keywords: Vincristine, peripheral neuropathy, vitamin E

BACKGROUND

There has been an increase in the survival of children with cancer over the last several decades. To a large extent this is due to new chemotherapeutic agents and improved treatment protocols, as well better management of the haematological side effects of chemotherapy. However, several long term complications continue to complicate cancer treatment [1]. One of the important non-haematological side effects is peripheral neuropathy (PN). Chemotherapy Induced Peripheral neuropathy (CIPN) is a severe and potentially permanent side-effect of modern chemotherapeutic agents. CIPN may lead to withdrawal of treatment and compromise the clinical outcomes [2, 3, 4].

The reported incidence of CIPN varies from 30%-80% and that of severe PN 1.6 % to 7%. This variability may be due several factors including type of cytotoxic drug, duration of treatment, rate of infusion, cumulative dose, pre-existing PN, pharmacogenomics and co morbidities [5, 6, 7, 8]. Of the various chemotherapeutic agents used in the paediatric population, the vinca alkaloid - Vincristine is probably the most common agent to be associated with PN.

VINCRISTINE INDUCED PERIPHERAL NEUROPATHY (VIPN)

Vincristine (VCN) leads to dose dependent and potentially treatment limiting sensori-motor axonal neuropathy. There is inhibition of anterograde and retrograde axonal transport

due to microtubule damage [4, 6, 9, 10]. Recent studies have explored the various mechanisms of VIPN/CIPN and also identified molecular targets that may result in selective and innovative interventional strategies [11, 12]. Recent studies, outlined in **Table 1** have suggested that VIPN in children may be a significant problem [7, 13, 14, 15, 16, and 17].

The symptoms of CIPN/VIPN may be sensory (tingling, paraesthesia, pain, hypoesthesia), motor (cramps, twitching, weakness, wasting) and autonomic (constipation, diarrhoea, abnormal sweating, dizziness). The clinical signs include altered sensations of touch, pain, vibration, reduced muscle strength, decreased or loss of deep tendon reflexes and postural hypotension. Nerve conduction studies show reduced amplitude of the sensory action potential and the compound muscle action potential [2, 3, 4, 5]. In children, VIPN may show a motor predominance, whereas in adult CIPN, sensory impairment is more frequent [18].

VITAMIN E

Vitamin E deficiency syndromes lead to sensory motor axonal neuropathy similar to that seen in CIPN [19, 20]. Reduced levels of vitamin E have been demonstrated in patients on cisplatin, patients with cisplatin induced PN, humans with various cancers and in children with acute lymphoblastic leukaemia(ALL) [21,22,23,24,25]. Studies evaluating the effect of vitamin E supplementation on CIPN have shown mixed results with efficacy in some [26, 27, 28, and 29]. Supplementation trials with Vitamin E have shown it to be an effective antioxidant adjuvant therapy, during the initial period of treatment in children with ALL, Vitamin E does not appear to change the antitumor efficacy of chemotherapy [30, 31].

METHODS

AIMS

1. To determine the frequency, severity and type of peripheral neuropathy associated with vincristine therapy in children, both clinically and electrophysiologically.
2. To measure the levels of vitamin E in the blood before and after starting chemotherapy and determine if it plays a role in VIPN.

PATIENTS

Children with newly diagnosed cancer whose chemotherapy protocol included vincristine and vinblastine were enrolled for the study. The patients were treated at the oncology unit at Princess Margaret Hospital, the only tertiary centre in Western Australia.

STUDY DESIGN

Ethics approval was obtained from the Human Research Ethics Committee at Princess Margaret Hospital.

A detailed history was obtained. This focused on motor and sensory symptoms including pain, tingling, numbness, paraesthesia, weakness and autonomic features like excessive sweating, constipation, diarrhoea. Dietary history was obtained by recall.

A specifically tailored **clinical and neurological examination** was conducted looking at the various parameters for evaluation of the peripheral nervous system. These included general clinical examination (including temperature, pulse rate, respiratory rate and blood pressure). Documented postural drop in the blood pressure with dizziness was considered positive for orthostatic hypotension. Neurological examination included the cranial nerves (II to XII) and a detailed sensory motor assessment including light touch, pin prick, 2 point discrimination, proprioception, joint position sense, deep tendon reflexes (DTRs) and assessment of muscle strength based on Medical Research Council (MRC) classification. Gait assessment included heel and toe walking when possible. The motor and sensory examination was tailored to and interpreted in the context of the age of the child.

An objective assessment of light touch was also obtained (when possible) using a Touch –Test sensory evaluator (North Coast Medical, Inc, Morgan Hill, California). Five monofilaments representing an increasing degree of mechanoceptive (fine touch) insensitivity were used. These were the 2.83(0.07g of pressure), 3.61 (representing 0.4 g of pressure), the 4.31 monofilament (2.0 g), the 4.56 monofilament (4.0 g), and the 6.65 monofilament (300 g). Light touch was considered affected if the child was unable to perceive size 3.61 (in accordance with the information provided in the package insert) over the fingers and toes. Two point discrimination was tested using the 2 point discriminator. Vibration perception was assessed using a vibrating 128 Hz tuning fork over the halluces, medial and lateral malleoli and more proximally when appropriate. A portable (hand held) biothesiometer was used to determine the Vibration Perception Thresholds (VPT), when possible. The amplitude was gradually increased until the threshold of vibratory sensation was reached [32]. Vibration thresholds of < 10mV were considered normal. The symptoms and signs of peripheral neuropathy were documented at the scheduled assessments. A modified total neuropathy score was tabulated using the first seven items (clinical features only) of the Total Neuropathy Score Grading [33], as shown in **Table 2**.

ELECTROPHYSIOLOGY

NCS were performed in a standard fashion, with a controlled environment using surface electrodes on Dantec Keypoint machine. The median nerve was tested in the upper limb for both motor and sensory potentials and in the lower limb the deep peroneal nerve for motor and the sural nerve for sensory. For motor studies surface electrodes were placed on the abductor pollicis brevis for the median nerve and the extensor digitorum brevis for the deep peroneal nerve. For both sensory and motor conduction studies, supramaximal stimulation was given if tolerated. The data collected included the onset latency and amplitude of the compound muscle action potential (CMAP), the peak latency and amplitude of the antidromic sensory nerve action potential (SNAP). The distal latencies, nerve conduction velocities and F waves (where possible) were determined. The values were compared to normative data [34, 35].

VITAMIN E

Blood samples for Vitamin E levels were collected in heparinised tubes, protected from light and processed immediately after sampling. Vitamin E analysis was made by High Performance Liquid Chromatography and alpha tocopherol levels were measured in umol/L. The values were compared with age dependant norms.

TIMING OF ASSESSMENTS

The detailed history, clinical examination, PN assessment and the vitamin E levels were done at recruitment and again at around 3, 6 and 12 months from the onset of chemotherapy.

DETAILS OF THE CANCER

The diagnosis, the chemotherapeutic regime and doses, use of steroids and use of any vitamins or alternative treatments were recorded. The duration of therapy with VCN, the cumulative dose and the number of doses (at 1.5mg/m2) in relation to the timing of the assessments is shown in **Table 3**. Table 3 details the other chemotherapeutic agents also received by the child.

STATISTICAL ANALYSIS

Statistical analysis was undertaken using Stata 10, Statacorp, Lakeway Drive, Texas. After excluding the missing values, the means and standard deviations were calculated. The differences between the two means were detected using Paired T test. 95 % confidence intervals were determined with a p value of <0.05 considered statistically significant.

RESULTS

30 patients were enrolled over a period of 12 months. One child with ALL withdrew from the study and 1 with brain tumour died. The remaining 19 boys and 9 girls had a mean age of 6.2 years, with a median of 5 (range 0.5-15.5). The data and analysis of the 28 patients who continued in the study are presented. 19 patients had acute lymphoblastic leukaemia (ALL): 15 with pre-B ALL and 4 had T cell ALL. Four patients had brain tumours, 3 Wilms' tumour and one each - rhabdomyosarcoma, non-Hodgkin's Lymphoma (NHL), Hodgkin's Lymphoma (HL) and Langerhans cell histiocytosis.

None of the patients had clinical or electrophysiological evidence of peripheral neuropathy at enrolment. 27 patients received vincristine, one was on vinblastine. Three patients also received platinum analogues: carboplatin - 2, cisplatin and carboplatin – 1. All children except one child were recruited prior to or within two weeks of starting chemotherapy. One child could not be recruited at baseline; his first assessment was at 3 moths. As can be seen in Table 3, seven children received VCN for 6 months only, the rest were still on VCN at 12 months' follow-up. The cumulative dose of VCN is shown in Table 3.

VIPN (TABLES 4 AND 6)

The most common motor symptom was distal weakness, seen in 39% at 3 months. This improved with time and at 12 months none of the patients complained of weakness. One child had proximal weakness that may have been due to steroid use.

Pain and paraesthesia were seen in 36% at 3 months; this improved at 6 and 12 month assessments. Autonomic features mainly in the form of constipation was seen in 43% at 3 months follow up. None of the children were reported to be constipated at the time of enrolment.

Abnormalities in deep tendon reflexes were seen in the majority of children. The most common sign was the loss of ankle deep tendon reflex seen in 57% patients at 3 months. Cranial neuropathy was seen in 1 child. Overall 80% of the patients had loss or reduced ankle deep tendon reflexes, 75% had lost or reduced knee reflexes and 40% had involvement of the upper limb reflexes, during the study.

Unsteadiness was seen in 11 patients at 3 months with persistence in four at 12 months. Most patients with unsteadiness had clinical evidence of PN. However, we did not include unsteadiness as a feature of PN, as three of these children had brain tumours and their CNS involvement could have been causative.

Biothesiometer: This was undertaken in 16 patients older than 5 years: the threshold was normal (<10mV) in all. Children younger than 5 tolerated the test but could not cooperate.

The modified total Neuropathy scores based on seven clinical items is shown in Table 2. VCN was discontinued in the child with the highest score with significant improvement subsequently.

ELECTROPHYSIOLOGY (TABLES 5AND 6)

NCS were obtained at baseline in 13 patients: in 12 at 3 months, in 7 at 6 and in 10 at 12 months. Overall 67 nerves were tested. We studied the median motor in 22 patients, the median sensory nerve in 15, the common peroneal nerve in 17 and sural nerve in 13 patients. F waves were attempted and reproducibly obtained in only 5 patients. 15 patients had at least one follow up NCS of which 13 (87%) were abnormal. The remaining 2 patients who had normal NCS on follow up, had clinical evidence of peripheral neuropathy. We summarise the abnormalities seen on NCS in Table 6. These include decrease in Compound Muscle Action Potential (CMAP), increase in distal latency, and reduction in nerve conduction velocity. The most common nerve affected was the deep peroneal with reduced CMAP in 82 % patients. Not surprisingly the motor and sensory nerves of the lower limbs were more affected.

Overall 26 of the 28 patients (93%) had evidence of VIPN clinically or electrophysiologically. The onset was early and before 3 months in the majority of the patients. The severity was clinically mild in most cases.

VITAMIN E (TABLE 7)

The levels of vitamin E remained in the normal range throughout the study however the values reduced from the baseline value and this drop in Vitamin E level (from baseline) was statistically significant at 3, 6, and at 12 months of chemotherapy. No other measures of nutrition were analysed.

DISCUSSION

Peripheral neuropathy is a common and at times dose-limiting adverse effect of vincristine therapy but may be under recognised and under diagnosed in children. The incidence varies in different studies because of different forms of assessments used and time frames involved [9,13,33,38,39,40,41,42,43]. We found VIPN occurred in the majority of children with 93% showing evidence of neuropathy either on clinical assessment or electrophysiology or both, similar to what has been reported by Lavoie-Smith et al [7].

On clinical assessment constipation, pain and weakness were the most common symptoms reported by 39-43% of children on at least one assessment. As young children may not be able to describe or report these symptoms, this may be an underestimation. Constipation occurs commonly in childhood, with reported incidence varying from 0.7-29.6% [44]. None of the children in the study reported constipation at the first assessment, it is therefore likely that in our group VIPN was contributory, though dietary changes, fluid status; other drugs may have also been co-contributors. Inclusion of assessments such as bowel patterns, dietary intake, may

have provided additional information regarding constipation in VIPN.

Clinically motor impairment seemed to occur in VIPN more frequently than sensory. Weakness was the most common motor symptom reported. Loss or reduced deep tendon reflexes was the most common sign elicited during our study. Nerve conduction studies showed abnormality in in 87% of the children who had at least one follow up electrophysiological assessment, similar to that reported in the study by Cortamanche et al [18]. Jain et al undertook a cross sectional study of survivors of ALL aged 5-18, within 3 years of completion of chemotherapy and found abnormalities on electrophysiological testing in 34% only. Perhaps the peripheral neuropathy and NCS improve with time. Reduced CMAP of the peroneal nerve was the most frequent abnormality in our study; this was similar to what Jain et al reported [13].

VIPN scores such as the paediatric modified total neuropathy score, with parameters similar to what we used have been developed and shown to be useful [9,33,38,43]. The NCS and spectrum of parameters measured in different studies has varied. We used a modified version of the Total Neuropathy Score Grading, as we did not have the NCS parameters that were used in Smith et al's grading system [33].

We are unable to evaluate the relationship between cumulative dose of vincristine and neuropathy, due to the small numbers in our study, variable duration of vincristine therapy and not all electrophysiology assessments being available at 3, 6 and 12 months follow-up, Our impression is that VIPN can occur quite early after starting therapy (<3 months), however with our protocol, we cannot be more precise. Platinum agents are known to cause PN and hence could have contributed to the incidence or severity of VIPN in the three children who received them.

VIPN is similar to the neuropathy seen in vitamin E deficiency disorders. It is interesting to note the drop in mean Vitamin E levels in our study. This may have been due to altered intake, reduced absorption, or increased loss. With the assessments and information we analysed, we are unable to determine what caused the levels to reduce. However, as the levels were in the normal range through the study, Vitamin E is unlikely to have played a significant role in the VIPN.

Our study is one of the few that assessed VIPN clinically and electrophysiologically during the first year of chemotherapy. It is important to know about VIPN/CIPN early to optimise management.

An important finding from this study is that, clinical tools alone may be quite reliable for diagnosis of VIPN in the first year of chemotherapy: all children who had abnormal NCS also had evidence of PN on clinical assessment. As NCS are difficult to undertake in sick, young children, they could be reserved for the atypical or severe case.

Limitations of our study are the small numbers, the short duration, the pragmatic approach in undertaking tests- we scheduled them to coincide with oncology admissions or outpatient reviews. If children were unwell or unwilling, we omitted the NCS and hence the number of NCS undertaken was less than that planned in the original protocol.

CONCLUSIONS

VIPN occurred in the majority of children (93%) in our study. VIPN was detected both on clinical assessments as well as electrophysiologically. All children with abnormal NCS had PN on clinical assessment, suggesting clinical evaluation would be adequate to identify VIPN in most children and NCS can be used selectively. The neuropathy in most of our children was mild, with motor dysfunction, more frequently than sensory. Vitamin E levels remained in the normal range, though there was a significant drop in the mean values. The role of Vitamin E in VIPN in children needs to be further elucidated. Functional assessments of the clinical impact of the neuropathy on day to day life, evaluation of neuro-interventional and neuro-protective strategies, long term follow up of VIPN and its effects on quality of life, in survivors of childhood cancer, is essential.

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This study has been presented as a poster at the International Child Neurology ASM in Brisbane in 2012 and at the World Muscle Society Meeting in Perth, Australia, 2012.

Competing interests

None of the authors have any personal or financial competing interests.

Author Contributions

Dr Kava was involved in data collection, performance of nerve conduction studies, data analysis, literature review and writing of the manuscript. Dr Srinivasjois performed the statistical analysis. Professor Cole was involved in revising the manuscript. Dr Barry Lewis assisted in performing the biochemical analysis for vitamin E. Dr Walsh and Professor Nagarajan have contributed to the conception and design of the study, nerve conduction studies, data analysis, literature review and revision of the manuscript.

Table 1: VIPN in children on cancer chemotherapy

Year of publication	Author	No	Time of Enrolment	Type of Cancer	Duration of study	Age Range	Dose of VCN	PNS used	Clinically diagnosed VIPN	PN on electro-physiology	Vitamin E
2016	Gilchrist et al	52	At 6 months of VCR treatment	ALL/Lymphoma/Solid Non CNS tumours		5 -22 years	mean cumulative dose 17.5 ± 8.8 mg/m2; range: 4.0 -40.5 mg/m2	Gait analysis only	52/70	Not done	Not done
2016	Gilchrist et al	67	On treatment and 3-6 months post treatment	ALL/ lymphomas/ non-CNS solid tumours	6 months post treatment	5 -18 years	Initial cumulative dose in ALL 23.3mg /m2 ± 5.6	Yes	In ALL 86.5% (on treatment) 11.5%,(6 months post treatment)	Not done	Not done
2015	Lavoie Smith EM et al	109	At diagnosis	ALL	12 months	1-18 years	VCR 1.5 mg/m2 / dose COG trials	Yes	78%	Not done	Not done
2014	Jain et al	80	Within 3 years of chemotherapy completion	ALL	-	5-18 years	24 doses 1.4 mg/m2	Yes	13.8%	33.75% Symmetric motor axonal polyneuropathy	WNL
2013	Lavoie Smith EM et al	65	Prior to treatment	ALL	15 weeks	2-18 years	VCR 1.5 mg/m2 Mean cumulative dose at week 15:12.6 mg	Yes	84%	Not done	Not done

No = Number of children enrolled
ALL = Acute Lymphoblastic Leukaemia
PNS = Peripheral Neuropathy Score
COG = Children's Oncology Group

Table 2: Modified version of the Total Neuropathy Score used for our study (mvTNS)

Clinical symptom/sign	**0**	**1**	**2**	**3**	**4**
Sensory symptoms	absent	only in fingers or toes	up to ankles/wrists	up to elbows and knees	above elbows and knees
Motor symptoms	absent	some difficulty but manages ADL	difficulty affecting ADL	requires assistance for ADL	severe weakness or paralysis
Autonomic symptoms	absent	one symptom	two symptoms	three symptoms	four and more symptoms
Response to pin prick	normal	reduced in fingers/toes	reduced in ankles or wrists	reduced to knees and elbow	reduced above knees and elbows
Response to vibration	normal	Reduced in fingers/toes	Reduced in ankles or wrists	Reduced to knees and elbows	reduced above knees and elbows
Muscle power(MRC)	normal	weakness in distal muscles with power 4/5	weakness in distal muscles with power 3/5 to 4/5	weakness up to knees or elbows with power <3/5	weakness above knees or elbows or power<2/5
Deep tendon reflexes	normal	decreased ankle reflex	absent ankle reflex (unilateral/bilateral)	absent ankle reflexes and reduced knee or upper limb reflexes	all reflexes absent

ADL = activities of daily living

Table 3: Details of cancer and chemotherapy

No	Age *	Diagnosis	Chemotherapeutic drugs	Duration (months)
1	10y3m	pre-B ALL	VCR,ARA-C,DEX,DNR,PEG,MTX	>12
2	4y5m	pre-B ALL	VCR,ARA-C, DEX, ADM, PEG, MTX, CTX, 6-TG	>12
3	2y8m	pre-B ALL	VCR,ARA-C, DEX, PEG, MTX	>12
4	11y11m	pre-B ALL	VCR,DNR,PEG,ARA-C,MTX, Pred	>12
5	1y2m	pre-B ALL	VCR,ARA-C,DEX,PEG,MTX	>12
6	4y9m	pre-B ALL	VCR,DEX,PEG,ARA-C,MTX,6-MP	>12
7	2y	pre-B ALL	VCR,ARA-C,DEX,PEG,MTX	>12
8	3y11m	pre-B ALL	VCR,ARA-C, DEX,PEG,MTX	>12
9	6y6m	pre-B ALL	VCR,ARA-C,DEX ,PEG,MTX	>12
10	11y	pre-B ALL	VCR,ARA-C,DEX,PEG,MTX	>12
11	10y9m	pre-B ALL	VCR,ARA-C,DEX, PEG,MTX	>12
12	6y	pre-B ALL	VCR,ARA-C, DEX ,PEG,MTX	>12
13	5y1m	pre-B ALL	VCR,ARA-C, DEX ,PEG,MTX	>12
14	2y10m	pre-B ALL	VCRARA-C, DEX ,PEG,MTX	>12
15	3y3m	T cell ALL	VCR, ARA-C, Pred ,DNR,PEG ,MTX	>12
16	5y11m	T cell ALL	VCR, ARA-C, Pred,DNR,PEG MTX	>12
17	11y11m	T cell ALL	VCR, ARA-C, Pred, DNR,PEG, MTX	>12
18	12y9m	T cell ALL	VCR, ARA-C, Pred, DNR, PEG, MTX	>12
19	3y3m	WT	VCR, DACT,ADM	6
20	6m	WT	VCR, DACT,ADM	6
21	5y11m	WT	VCR, DACT,ADM	6
22	1y2m	astrocytoma	VCR, CBDCA	>12
23	2y11m	ependymoblastoma	VCR, ETO, CTX, CDDP,CBDCA, thiotepa	5
24	4y4m	HL	VCR, ADM,BLEO, VP-16,Pred,CTX	>12
25	3y2m	LCH	Pred, VLB	6
26	4y2m	astrocytoma	VCR,CBDCA	>12
27	14y4m	NHL (brain)	VCR,CTX ,Pred, HC, MTX,ARA-C	6
28	4y11m	ERMS	VCR,DACT,CTX, DEX	7

*- age at diagnosis, y-years, m-months, ALL- acute lymphoblastic leukemia , pre-B-precursor B cell, WT-Wilms tumour, HL-Hodgkins lymphoma, LCH-Langerhans cell histiocytosis ,NHL-non Hodgkins lymphoma, ERMS-Embryonal Rhabdomyosarcoma, VCR-Vincristine, ADM-Doxorubicin, ARA-C-Cytarabine, Dex-Dexamethasone, DNR-Daunorubicin, PEG-L-asparaginase, VLB-Vinblastine, CBDCA-Carboplatin, CTX-Cyclophosphamide, Pred-prednisolone,6-MP-6 Mercaptopurine, MTX-Methotrexate, DACT-Dactinomycin, HC-hydrocortisone, CDDP-Cisplatin, ETO-Etoposide, BLEO- Bleomycin

Table 4: Motor, Sensory and Autonomic features of VIPN in 28 children

	3 months		6 months		12 months	
	N	(%)	N	(%)	N	(%)
Motor						
Subjective Weakness	11	(39)	1	(4)	0	
Objective Weakness	6	(21)	6	(21)	4	(14)
AJ lost	16	(57)	18	(64)	18	(64)
AJ reduced	6	(21)	3	(11)	3	(11)
KJ lost	8	(29)	11	(39)	6	(21)
KJ reduced	13	(46)	5	(18)	5	(18)
Upper limb DTR lost	3	(11)	2	(7)	4	(14)
Upper limb DTR reduced	8	(29)	9	(32)	4	(14)
Cranial Neuropathy	1	(4)	0		0	
Atrophy(wasting of muscles)	1	(4)	1	(4)	2	(7)
Subjective Sensory						
Pain(neuropathic)	10	(36)	3	(11)	2	(7)
Tingling	0		1	(4)	0	
Numbness	3	(11)	2	(7)	0	
Unsteadiness*	11	(39)	3	(11)	4	(14)
Objective Sensory Impairment	3	(11)	1	(4)	2	(7)
Autonomic						
Constipation	12	(43)	1	(4)	2	(7)
Orthostatic hypotension	1	(4)	0		0	
Excessive sweating	3	(11)	1	(4)	1	(4)

*Unsteadiness was not included in the final analysis of the incidence of neuropathy.

AJ = Ankle jerk, KJ = Knee jerk, DTR = Deep tendon reflex, N = number

Table 5: Findings of Nerve Conduction studies

Nerves tested	**Decreased Amplitude** Abnormal Number/total performed (%)	**Prolonged Distal Latency** Abnormal Number/total performed (%)	**Decreased Nerve Conduction Velocity** Abnormal Number/total performed (%)
Median (motor)	13/22 (59%)	10/22(45%)	6/22(27%)
Median (sensory)	7/15 (47%)	4/15(27%)	3/15(20%)
Peroneal(motor)	14/17 (82%)	7/17(41%)	1/17(6%)
Sural (sensory)	7/13(54%)	6/13 (46%)	4/13(31%)

Table 6: Clinical and electrophysiological features of peripheral neuropathy

	3 months				6 months			12 months			3 months				6 months				12 months			
No	NCS 0	NCS	VCR CD (mg)	VCR N o of doses	NCS	VCR CD (mg)	VCR No of dose	NCS	VCR CD (mg)	VCR No of doses	Symptoms	Motor signs	Sensory signs	mvTNS	Symptoms	Motor signs	Sensory signs	mvTNS	Symptoms	Motor signs	Sensory signs	mvTNS
1	N	abN	13.2	8	abN	23	12	abN	36.7	22	√	√	x	6	x	√	x	3	x	x	x	0
2	N	-	-	-	-	-	-	-	-	-	x	√	x	3	x	√	x	3	x	√	x	7
3	N	-	-	-	-	-	-	N	27.1	25	√	√	√	3	x	√	x	2	x	√	x	3
4	-	-	-	-	abN	32.3	17	abN	42	23	x	x	x	NA	√	√	√	5	x	√	√	3
5	N	abN	5.6	7	abN	10.4	13	-	-	-	x	x	√	2	x	x	x	0	x	√	x	3
6	N	abN	8.7	8	-	-	-	abN	23.5	15	x	√	√	2	x	√	√	2	x	√	√	5
7	-	-	-	-	-	-	-	-	-	-	x	√	x	1	x	√	x	3	x	√	x	2
8	-	abN	8.8	8	-	-	-	abN	30.6	27	√	√	√	7	x	√	x	4	x	√	x	1
9	-	abN	6.4	5	-	-	-	-	-	-	x	√	x	4	x	√	x	3	x	√	x	3
10	-	-	-	-	-	-	-	-	-	-	x	√	√	5	√	√	x	6	x	√	x	4
11	-	-	-	-	N	20	10	-	-	-	√	√	√	7	x	√	x	3	x	√	x	3
12	-	N	5.6	4	abN	17.7	13	N	33.8	24	√	√	√	6	√	√	x	4	x	√	x	3
13	-	-	-	-	-	-	-	-	-	-	√	√	x	4	x	√	x	3	x	√	x	2
14	-	abN	4	4	-	-	-	-	-	-	√	√	x	5	x	x	x	0	x	√	x	3
15	N	abN	6.2	6	-	-	-	-	-	-	x	√	√	6	√	√	x	6	x	√	x	2
16	-	-	-	-	-	-	-	abN	33	26	√	√	x	3	x	√	x	4	x	√	x	2
17	N	abN	22	12	abN	28	15	abN	50	25	x	√	√	2	√	√	x	5	x	√	x	6
18	-	-	-	-	-	-	-	-	-	-	x	√	x	4	x	√	x	3	x	√	x	2
19	-	-	-	-	-	-	-	-	-	-	x	√	x	3	x	x	x	0	x	x	x	0
20	-	-	-	-	-	-	-	-	-	-	x	√	x	2	x	x	x	0	x	x	x	0
21	-	abN	11.2	8	-	-	-	-	-	-	√	√	√	10	x	√	x	5	x	√	x	1
22	N	-	-	-	-	-	-	-	-	-	x	√	x	3	x	√	x	2	x	√	x	2
23	N	-	-	-	-	-	-	-	-	-	√	√	x	2	x	x	x	0	x	x	x	0
24	-	-	-	-	-	-	-	-	-	-	x	√	x	3	x	√	x	2	x	x	x	0
25	N	N	37.2 VLB	10	-	-	-	N	48.9 VLB	13	x	√	√	4	x	x	x	0	x	x	x	0
26	N	-	-	-	-	-	-	-	-	-	x	x	x	0	x	x	x	0	x	√	x	0
27	N	abN	5.7	3	abN	9.7	5	abN	9.7	5	√	x	x	1	√	x	x	1	x	√	x	5
28	N	-	-	-	-	-	-	-	-	-	x	√	x	3	x	x	x	3	√	√	x	2

Legends: No=patient number, NCS=nerve conduction studies,0=Baseline studies, VCR=Vincristine, VCR CD=Vincristine cumulative dose at the time of the NCS,VCR No of doses=Number of doses of Vincristine of 1.5mg/m2, N=normal, abN=abnormal, - = not done, x=absent, √=present, NA=not available, mvTNS=modified version of Total Neuropathy Score

Table 7 : Levels of vitamin E at baseline,3 months, 6 months and 12 months

	n	Mean	SD	95 % CI	P
Baseline	23	32.87	15.04		
3 months	26	23.03	8.17		
6 months	21	24.24	8.42		
12 months	21	20.33	4.27		
change at 3 months	23	-10.17*	11.76	-15.25995 -5.087875	0.0004
Change at 6 months	18	-10.44*	13.87	-17.34398 -3.544908	0.0053
Change at 12 months	19	-11.89*	17.79	-20.46855 -3.320927	0.0092

*Presented as mean difference with the baseline value of Vitamin E. (alpha tocopherol levels in umol/L).

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