Acta Haematologica Polonica 2024
Number 1, Volume 55, pages 42–47
DOI: 10.5603/ahp.97241
ISSN 0001–5814
e-ISSN 2300–7117

ORIGINAL RESEARCH ARTICLE

VIA MEDICA

Incidence and clinical spectrum of vincristine-induced peripheral neuropathy in patients with acute lymphoblastic leukemia: a prospective study of 29 cases

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Abstract

Introduction: Vincristine is used in many therapeutic schemes of oncological treatment in children, and one of its common complications is neurotoxicity. The aim of this study was to assess the incidence of vincristine-induced polyneuropathy in children treated for acute lymphoblastic leukemia. Secondly, we evaluated the clinical spectrum of chemotherapy-induced peripheral neuropathy.

Material and methods: The study included 29 patients with newly diagnosed acute lymphoblastic leukemia who were treated according to the ALL IC-BFM 2009 therapeutic program. The study was designed for the induction remission phase, in which patients received unified anticancer treatment. A neurological assessment was performed on days 1, 8, 15, 22, 29 and 36 of treatment, and consisted of an original questionnaire completed by patients or their caregivers, a physical examination, and a neurological examination. Abnormalities were assessed according to the Common Terminology Criteria for Adverse Events, version 5.0 scale.

Results: Symptoms of polyneuropathy occurred in 25 patients (86.2%). Motor neuropathy was the most common type of polyneuropathy in the examined group. In half of the cases, the polyneuropathy was severe, rated at 3 or 4 points. The most serious course manifested itself in three patients in severe gastrointestinal ileus with subsequent intestinal perforation. In another case, rated at 4 points, breathing disorders occurred with apnea episodes.

Conclusions: Vincristine-induced polyneuropathy is common in children with acute lymphoblastic leukemia in the induction of remission phase, and is severe in half of cases. In the pediatric population, in contrast to adults, vincristine-induced polyneuropathy motor symptoms are predominant.

Keywords: vincristine, neuropathy, acute lymphoblastic leukemia, children

Acta Haematologica Polonica 2024; 55, 1: 42–47

Introduction

The most common cancer in children is acute lymphoblastic leukemia (ALL), with the highest incidence rate found in the age range of 2–5 years (6.2/100,000 children/year). The number of new cases decreases with age from 2.7/100,000/year at age 5–9 to 1.6/100,000/year at age 10–14 [1]. According to the recommendations of the Polish Pediatric Group for the Treatment of Leukemia and Lymphoma, until March 2018 the management of acute lymphoblastic leukemia in children in Poland was carried out according to the ALL International Cooperative

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Received: 03.09.2023 Accepted: 30.10.2023 Early publication: 21.01.2024

Berlin–Frankfurt–Münster 2009 (ALL IC-BFM 2009) therapeutic program. This program is based on four phases: remission induction, consolidation, remission reinduction, and maintenance therapy, in parallel with prevention or treatment of central nervous system (CNS) leukemia.

One of the common complications of anti-cancer treatment is neurotoxicity of cytotoxic drugs. Chemotherapy-induced peripheral neuropathy (CIPN) involves neuronal damage due to drugs such as vinca alkaloids, platinum derivatives, taxanes, and proteasome inhibitors [2]. The diagnosis of CIPN is confirmed by the demonstration of a causal relationship between the drug used and the symptoms of neuropathy, and the key diagnostic criteria include determining the time correlation between neuropathy symptoms and treatment, and achieving clinical improvement after discontinuation of the substance [3].

Vincristine (VCR) is used in many therapeutic schemes of oncological treatment in children. In the treatment of acute lymphoblastic leukemia, it is used in the induction and reinduction phases. The site of action of VCR is the microtubules (MTs), on which three binding regions can be distinguished: the vinca alkaloid domain, the colchicine domain, and the paclitaxel domain. Various chemicals bind to specific sites, stabilizing or destabilizing microtubules [4]. Vincristine belongs to the group of polymerization inhibitors. It forms a binding with β-tubulin, thus preventing its polymerization with α-tubulin into microtubules [5]. This inhibits mitosis, and interferes with intracellular transport and cell motility. Therefore, vincristine belongs to the group of phase-specific cytostatics, inhibiting cell division at the metaphase stage (M phase) [6]. Vincristine has a high affinity to peripheral microtubules (so-called 'end poisons'), and a low one to tubulin cytoskeleton [7].

The aim of this study was to assess the incidence of vincristine-induced polyneuropathy in children treated for acute lymphoblastic leukemia. Secondly, we evaluated the clinical spectrum of CIPN in patients treated according to the ALL IC-BFM 2009 protocol.

Material and methods

The study was prospective. 29 patients diagnosed in the Department of Paediatric Hematology, Oncology and Transplantology in the Children's Hospital of Lublin, Poland from 2015 to 2018 were included. The patients were treated according to the ALL IC-BFM 2009 therapeutic program. The study was designed for an induction remission phase in which patients received a unified anticancer treatment consisting of prednisone, vincristine, daunorubicin (DNR) and L-asparaginase at standard doses, calculated per square meter of body surface area.

Inclusion criteria were: newly diagnosed acute lymphoblastic leukemia, treatment according to the ALL IC-BFM 2009 therapeutic program, written consent from caregivers or from patients over 16 years of age, and achieving 15 points on the Glasgow Coma Score in the control points. Exclusion criteria were: a history of neuropathy, symptoms of neuropathy on day 1 of treatment according to the ALL IC-BFM 2009 protocol, previous anticancer treatment, previous treatment with cytostatics or steroids over 1 mg/kg body weight over two weeks, a history of epilepsy or other neurological diseases, a history of CNS trauma, a history of neuroinfection, the use of drugs inducing neuropathy within the six months prior to diagnosis, diabetes mellitus, renal failure, and systemic connective tissue disease diagnosed before starting the treatment according to ALL IC-BFM 2009.

A neurological assessment was performed on the day of starting treatment ('day 1' acc. to ALL IC-BFM 2009), on each day of intravenous VCR (days 8, 15, 22, and 29), and again seven days after the last dose of VCR (day 36). It consisted of a questionnaire completed by patients or their caregivers, a physical examination, and a neurological examination.

An original questionnaire consisting of questions directly addressed to the patients was designed for this study. For those children unable to answer due to age, speech disorder, or a lack of willingness to cooperate, the survey was addressed to their caregivers. In addition, pain was assessed by patients according to the visual analog scale VAS (Table I).

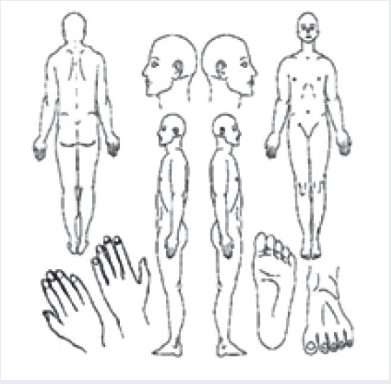
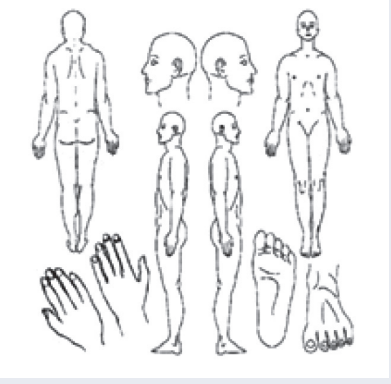
The physical examination was a standard pediatric examination with anthropometric measurements (weight, height), a consciousness assessment and a neurological examination. Abnormalities in the neurological examination were assessed according to the Glasgow, Lovett, and Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) scales.

Ethical approval was obtained from the Ethical Committee of the Medical University of Lublin (no. KE-0254/333/2015) and written consent was obtained from all subjects. The datasets used and analyzed during the current study are available from the authors upon request. Data was analyzed using Microsoft Excel computer software.

Results

The patients' ages at diagnosis were 1.25 to 17.65 years [median 4.5, mean 6.65, standard deviation (SD) ± 5 months). In the study group, there were 16 boys (55.17%) and 13 girls (44.83%). The most frequently diagnosed leukemia was from precursors of lymphocytes B (24 persons, 82.75%), less often from T lymphocytes precursors (four persons, 13.8%), and there was only one case of ALL with acute myeloid leukemia (AML) coexpression (3.45%). All patients who qualified for the study completed it. After 33 days of treatment, the children were classified into three risk groups, among which the intermediate risk group was the largest (19/29 patients, 65.52%), the high risk group

Table I. Questions in questionnaire

Questions directly addressed to patients	Questions addressed to caregivers
Do you have the following symptoms? 1. Pain (if yes, give its intensity on the VAS scale) 2. Tingling, numbness 3. Loss of feeling — heat/cold, touch 4. Difficulty holding small items such as a pen 5. Difficulty with buttoning, lacing shoes 6. Swallowing problems 7. Problems/pain when biting 8. Constipation 9. Difficulty urinating 10. Problems with walking 11. Problems with getting out of bed *Mark ailment on diagram: 	Does your child have (or do you suspect he/she has) the following symptoms? 1. Pain 2. Difficulty holding small items that he or she has previously held 3. Problems with swallowing 4. Bites reluctantly 5. Is constipated 6. Is less active 7. He/she does not perform activities that he/she has done so far, or does them "awkwardly" or with difficulty, such as sitting, crawling, walking, grabbing objects, turning from their back onto their tummy and vice versa *If you know location, mark symptoms on diagram: 

had eight patients (27.59%), and there were two patients (6.89%) in the standard risk group. The predominant age of patients was under 5 years in each group of patients assessed in the study. The number of patients in each risk group, taking gender into account and depending on the severity of polyneuropathy, is summarized in Table II.

Symptoms of polyneuropathy occurred in 25/29 patients (86.2%). Motor neuropathy with concomitant gait disturbance was the most common type of polyneuropathy in the examined group. The most serious course manifested itself in severe gastrointestinal ileus with subsequent intestinal perforation in three patients. In another case, rated 4 points on the CTCAE v.5.0 scale, breathing disorders occurred with apnea episodes. Symptoms observed in patients are set out in Table III.

The most common polyneuropathy in this group was that assessed as 3 points (11 people, 37.93%) and that assessed as 2 points (nine people, 31.03%), according to the CTCAE v.5.0 scale. Less frequently we observed patients without symptoms of polyneuropathy or with severe polyneuropathy rated 4 points (a total of four patients, 13.8%). In one case, the maximum intensity of symptoms reached 1 point (3.44%).

Table II. Numbers of patients in each risk group according to gender and polyneuropathy severity

CTCAE v.5.0 (points)	Risk groups		
	SR	IR	HR
0	0	1 (M)	3 (F — 2, M — 1)
1	0	0	1 (M)
2	1 (F)	7 (F — 3, M — 4)	1 (M)
3	0	8 (F — 4, M — 4)	3 (F — 2, M — 1)
4	1 (M)	3 (F — 1, M — 2)	0
5	0	0	0

CTCAE v5.0 — Common Terminology Criteria for Adverse Events version 5.0; SR — standard risk; IR — intermediate risk; HR — high risk; F — female; M — male

Table III. Assessment of polyneuropathy in study group according to Common Terminology Criteria for Adverse Events version 5.0 scale based on neurological examination and questionnaires

Patient number	Motor neuropathy	Sensory neuropathy	Cranial nerve neuropathy	Autonomic neuropathy	Gait disturbance	Pain	Max number of points in study
1	0	0	0	0	0	0	0
2	3	2	3[a]	0	2	3	3
3	3	2	0	3[b]	3	2	3
4	0	0	0	1[b]	1	0	1
5	3	0	0	0	3	2	3
6	0	0	0	0	0	0	0
7	3	0	0	2[b]	3	2	3
8	0	0	0	0	0	0	0
9	3	2	2[a]	1[b]	3	3	3
10	0	0	0	0	0	0	0
11	3	2	0	0	3	3	3
12	3	2	0	0	3	3	3
13	4[c]	2	0	2	3	2	4
14	2	1	0	0	2	1	2
15	2	0	0	0	2	1	2
16	3	2	0	4[b]	3	3	4
17	2	2	0	0	2	1	2
18	2	1	0	0	2	0	2
19	3	2	0	4[b]	3	3	4
20	2	2	0	0	2	2	2
21	3	2	2[d]	0	3	1	3
22	2	2	0	2[b]	2	0	2
23	1	1	0	2[b], 3[e]	1	2	3
24	2	2	0	4[b]	2	3	4
25	2	2	0	0	2	1	2
26	2	1	0	2[b]	2	2	2
27	2	2	0	2[b]	2	1	2
28	3	2	0	0	3	3	3
29	3	2	0	0	3	2	3

[a]V nerve polyneuropathy; [b]gastrointestinal polyneuropathy; [c]respiratory polyneuropathy; [d]III nerve polyneuropathy; [e]polyneuropathy of urinary system

Discussion

The use of chemotherapy in the treatment of acute lymphoblastic leukemia in children has brought a significant increase in the number of cured patients. Due to the low therapeutic index, cytotoxic drugs may cause many complications, including life-threatening ones. The occurrence of CIPN has been estimated at 40–90% of patients in available publications, with the varying frequencies depending on the substances used and the therapeutic regimen, as well as on the type of scale used to assess the severity of symptoms [8–11].

This prospective study confirmed a high incidence of CIPN among pediatric patients with acute lymphoblastic leukemia. It was observed in 86.2% of the study group. The results differ from those in the available literature, because the most common rating in this study was 3 points. Differences mainly concern the most serious complications, estimated at 3 or 4 points, the frequency of which in other publications has been lower and has ranged from 0–13%. **In one study, a World Health Organization (WHO) neurotoxicity score was estimated and vibration sense and electrophysiological measurements were taken at standardized times during vincristine treatment. The WHO neurotoxicity score showed decreased, or the disappearance of, Achilles tendon reflexes, plus mild sensory disturbances, but grade 3–4 neurotoxicity was not demonstrated by any of the**

children. These differences could be the result of qualification of patients with a cancer other than acute lymphoblastic leukemia, the use of different therapeutic regimens, the number of patients included, or the determination of different time points of neurological examination [12–14]. In this study, motor polyneuropathy was the most frequently diagnosed complication, and sensory discomfort was less common. Similar results have been presented by other researchers, who have confirmed that in the pediatric population, in contrast to adults, CIPN motor symptoms dominate [15, 16].

Chemotherapy-induced peripheral polyneuropathy in children with acute lymphoblastic leukemia is most often caused by vincristine, but can also be caused by the use of vindesine and in very rare cases (less than 1/10,000) by ifosfamide, cyclophosphamide or high doses of cytarabine, but these drugs were not used in our study [17–19]. Our choice of the induction phase of remission as the study period (Protocol IA acc. to ALL IC-BFM 2009) was optimal in our opinion, as the influence of other factors on test results was minimal. The patients in the study group received unified treatment, except for two from the standard risk group who received two doses fewer of daunorubicin than other patients. However, it seems that this difference could not affect the final result, as there is no evidence that DNR causes polyneuropathy or affects VCR metabolism [20]. In other phases of treatment, differences resulting from the combination of the used cytotoxic drugs could be significant. In addition, in the first 33 days of therapy, treatment was generally conducted without delays. Only severe and life-threatening complications could be a contraindication to chemotherapy. In this study, four patients developed polyneuropathy symptoms rated at 4 points on the CTCAE v5.0 scale and their treatment was delayed, but after day 36 of the induction phase.

Non-cytotoxic drugs that are metabolized by P450 CYP3A may affect the severity of neuropathy symptoms. These medicines include antibiotics (erythromycin, clarithromycin, ciprofloxacin, chloramphenicol), antifungal drugs (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole), antiviral drugs (ritonavir, nelfinavir), calcium channel blockers (amlodipine, nifedipine), and anti-epileptic drugs (valproic acid) [4, 6, 21, 22].

During this study, of the above mentioned only fluconazole was used as prophylaxis. It has been demonstrated in many publications that fluconazole at doses above 200 mg daily is a weak inhibitor of P450 CYP3A, compared to other azoles. In addition, no statistical association has been observed between the severity of polyneuropathy and the concomitant use of fluconazole and vincristine [23–25]. For these reasons, this antifungal drug is preferred for patients undergoing leukemia treatment at an early stage.

Nowadays, there are no effective therapeutic methods for the management of chemotherapy-induced peripheral polyneuropathy in clinical trials. CIPN treatment is only symptomatic with analgesics, sometimes a reduction of the VCR dose or discontinuation of the drug. This could extend the therapeutic process and may lead to recurrence of the disease. Physiotherapy does not affect the course of neuropathy, but prevents muscle contracture and atrophy [26]. Many different neuroprotective substances have been used for CIPN therapy in children, e.g. carbamazepine, glutamic acid, intravenous immunoglobulins, pyridoxine, pyridostigmine and gabapentin. The effects of such treatment and prevention have been variable, and they have usually proved unsatisfactory. Retrospective studies have identified positive effects of these substances, but naturally-occurring spontaneous remission and recovery cannot be ruled out [26–29]. According to the guidelines of the American Society of Clinical Oncology (ASCO), duloxetine, which belongs to the group of selective serotonin and norepinephrine reuptake inhibitors (SSNRIs), is recommended for adults only. Other potential neuroprotective substances used in experimental studies have been: folinic acid, vitamin B1, vitamin B6, glutamic acid, Org 2766 [synthetic analogue of adrenocorticotropic hormone (ACTH) 4–9], insulin-like growth factor, and nerve growth factor [3, 6, 26]. In our study, only rehabilitation and analgesic nonsteroidal anti-inflammatory drugs were used in children with symptoms of polyneuropathy.

Conclusions

Vincristine-induced polyneuropathy is common in children with acute lymphoblastic leukemia **in the induction of remission phase**, and is severe in half of cases. In the pediatric population, in contrast to adults, CIPN motor symptoms are predominant.

Article information and declarations

Acknowledgments
Not applicable.

Author contributions
MC and KD conceived idea. MC performed examinations and computations. MC and KD verified analytical methods. MC and KD contributed to interpretation of results. MC wrote manuscript with support from KD. Both authors discussed results and contributed to final manuscript.

Conflict of interests
The authors declare no conflict of interests.

Data availability statement
The datasets used and analyzed during the current study are available from the authors upon request.

Ethics statement

Ethical approval was obtained from the Ethical Committee of the Medical University of Lublin (no. KE-0254/333/2015) and written consent was obtained from all subjects.

Funding

This work was supported by the MN SD 460 grant of the Medical University of Lublin.

Supplementary material

None.

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