Review Article
Vincristine-induced peripheral neuropathy in pediatric cancer patients

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Abstract: Vincristine is a chemotherapeutic agent that is a component of many combination regimens for a variety of malignancies, including several common pediatric tumors. Vincristine treatment is limited by a progressive sensorimotor peripheral neuropathy. Vincristine-induced peripheral neuropathy (VIPN) is particularly challenging to detect and monitor in pediatric patients, in whom the side effect can diminish long term quality of life. This review summarizes the current state of knowledge regarding VIPN, focusing on its description, assessment, prediction, prevention, and treatment. Significant progress has been made in our knowledge about VIPN incidence and progression, and tools have been developed that enable clinicians to reliably measure VIPN in pediatric patients. Despite these successes, little progress has been made in identifying clinically useful predictors of VIPN or in developing effective approaches for VIPN prevention or treatment in either pediatric or adult patients. Further research is needed to predict, prevent, and treat VIPN to maximize therapeutic benefit and avoid unnecessary toxicity from vincristine treatment.

Keywords: Vincristine, peripheral neuropathy, prevention, assessment, pharmacogenetics, pediatric oncology

Introduction

The vinca alkaloids are a class of agents originally derived from the Madagascar periwinkle plant and historically utilized in diabetic patients for their presumed hypoglycemic effects. In the late 1950's, it was realized that certain vinca alkaloids caused bone marrow suppression in mice as well as prolongation of life in rats with acute lymphoblastic leukemia (ALL) [1]. Subsequently, this class of anti-mitotic agents has become extensively incorporated into multi-agent chemotherapy regimens for a vast number of malignancies including ALL, lymphomas, sarcomas, neuroblastoma, and kidney, liver, lung, brain and breast tumors amongst others. Additionally, immunosuppressant effects have led to their use in idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura. Vincristine, the most commonly used vinca alkaloid in pediatric patients, frequently has dose-limiting neurotoxicity which can be devastating; not only

leading to severe motor and sensory peripheral neuropathies affecting quality of life, but also contributing to treatment delays and dose reductions. This review will focus on describing vincristine-induced peripheral neuropathy (VIPN), and summarizing the available literature around assessing, predicting and treating this adverse effect in pediatric patients.

Clinical use

Vinblastine (VBL) and vincristine (VCR) were the first two vinca alkaloid compounds to be successfully incorporated into chemotherapy regimens. These agents work by arresting dividing cells in metaphase by binding to the β-subunit of tubulin heterodimers to prevent polymerization and incorporation into microtubules [2]. In more recent decades, vindesine and vinorelbine have come to market as semi-synthetic vinca alkaloids. Vindesine has similar antitumor activity as vincristine, but increased myelosuppression and lack of clear improvement in neu-

ropathic adverse events has limited its clinical usefulness [3]. Vinorelbine, on the other hand, is composed of an eight-member catharnine ring, as opposed to the nine-member rings of the other vinca alkaloids, which allows for increased capacity to bind to mitotic spindles over axonal microtubules, leading to decreased neurotoxicity with this agent [4]. Vinorelbine is most commonly used to treat breast and non-small cell lung cancers and myelosuppression is its dose-limiting side effect. Finally, vincristine has most recently been encapsulated in sphingomyelin and cholesterol nanoparticles as a vincristine sulfate liposome injection (VSLI) and marketed under the trade name Marqibo. This new formulation of vincristine was designed to allow for optimized pharmacokinetics, enhanced drug delivery to tumor tissues, and to allow for dose intensification [5]. It was FDA-approved in 2012 for the treatment of adult patients with relapsed/refractory Philadelphia-chromosome negative acute lymphoid leukemia.

Vincristine has poor oral bioavailability and is formulated for intravenous administration as vincristine sulfate. Vincristine sulfate is a vesicant and is fatal if given intrathecally. After intravenous administration, vincristine rapidly distributes extensively into most body tissues; however, there is poor penetration across the blood brain barrier (BBB) and into the central nervous system (CNS). The liver is primarily responsible for the metabolism of vincristine, which is a substrate for the cytochrome P450 3A (CYP3A) enzyme system, particularly CYP3A4 and CYP3A5, making it susceptible to drug-drug interactions and interpatient variability in metabolism [6, 7]. Dosing adjustments should be made in the presence of hyperbilirubinemia, particularly elevated direct bilirubin. Vincristine has a long terminal half-life of 85 hours and is primarily eliminated in the feces. Vincristine is rarely myelosuppressive and can often be administered even in the presence of leukopenia and thrombocytopenia [8].

Description of vincristine-induced peripheral neuropathy (VIPN)

Peripheral neuropathy is a well-known side effect of several classes of chemotherapy including the vincas, taxanes (paclitaxel and docetaxel), and platins (cisplatin, carboplatin, oxaliplatin). As described previously, the vincas

(and taxanes) target the β-tubulin subunit of microtubules, which are critical components of nerve fiber axons. Due to the affinity of the vincas for both mitotic spindles and axonal microtubules, particularly with vincristine, these agents cause axonopathy that manifests as a slowly progressive axonal sensorimotor neuropathy [9, 10]. Several additional mechanisms for vinca-induced peripheral neuropathy (VIPN) have been proposed from mechanistic work in cellular and animal models [11, 12] and the exact mechanism is still not completely understood.

VIPN is experienced by nearly all children who receive vincristine treatment [13-15]. The incidence and severity varies based on a variety of risk factors, as described in section 5. Signs and symptoms of VIPN generally fall into three main categories: sensory, motor, and autonomic neuropathy [14, 16-18]. Common characteristics of sensory neuropathy include numbness, tingling, and neuropathic pain experienced bilaterally in the upper and lower extremities. In most cases, VIPN progresses distally to proximally; signs and symptoms often first appear in the toes and feet, and as neuropathy worsens, clinical abnormalities become evident more proximally within the foot, ankle, and leg, followed by the fingers and hands. Children who receive vincristine become less able to detect light touch, pinprick sensations, vibration, and differences in temperature when hot or cold objects are applied to the skin. Although less common, some patients report hoarseness and jaw pain due to vincristine's damaging effects on cranial nerves. Hyporeflexia, loss or reduction in deep tendon reflexes, provides evidence of both sensory and motor VIPN. Common motor neuropathy signs and symptoms include foot-drop and upper and lower extremity weakness. Indicators of autonomic neuropathy include constipation, urinary retention, and orthostatic hypotension [19, 20].

When evaluating VIPN patterns over time, several interesting findings become evident. In the first year of vincristine therapy for ALL, hyporeflexia is the most common and severe VIPN manifestation, followed by decreased vibration sensibility and strength [14]. Signs and/or symptoms can emerge within a week of initiating vincristine therapy and continue to worsen even after vincristine dosing and frequency is decreased, known as the coasting effect [14].

VIPN severity can remain unchanged for up to 12 months following dose reduction [14], and can persist for years beyond treatment completion [15].

Assessment

Although peripheral neuropathy is a well-recognized side effect of vincristine therapy, VIPN characteristics, severity and incidence patterns, and the long-term consequences of VIPN on function and quality of life (QOL) in children are not well-understood. This dearth of knowledge is directly linked to the lack of widely-accepted, comprehensive, reliable, valid, and clinically feasible VIPN assessment approaches for use in pediatric populations. What follows is a brief overview of VIPN assessment techniques, and the benefits and challenges associated with their use (see **Table 1**).

There are several measurement tools that can be used to assess peripheral neuropathy in adults receiving neurotoxic drugs [21-24], and in children with neuropathy secondary to other diseases such as diabetes [25-29]. However, there are few VIPN measurement tools that have been optimized for use in pediatric oncology settings [14, 16, 30, 31]. Grading scales, such as the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), are commonly used to provide a numeric score reflecting sensory and motor neuropathy severity [14]. When using these scales, a score of "0" reflects no neuropathy and a score of "5" equates to death caused by neurotoxicity. Although the NCI-CTCAE and other similar grading scales are familiar to clinicians and easy to use, several studies provide compelling evidence that these scales are marginally reliable, valid, sensitive, and responsive to change over time [16, 32-35]. For example, Gilchrist et al. reported that NCI-CTCAE scores fail to detect 40% and 15% of sensory and motor neuropathy deficits, respectively.

Since vincristine damages both small and large nerve fibers involved with sensory, motor, and autonomic function [17], the best measurement approach should incorporate objective and subjective assessments that quantify damage to both fiber types [22, 23, 32]. Vincristine causes abnormally diminished sensory and motor nerve conduction amplitude, with motor nerves showing the most significant changes

[15, 18, 36]. Objective measures should be used to uncover pre-clinical signs of early-onset neuropathy that cannot be detected by the patient. When evaluating large nerve fiber function, oncology clinicians typically focus on assessing deep tendon reflexes and strength. Reflex assessment is the most feasible approach because it is quick to complete and can usually be conducted even with very young children. Testing the patient's ability to feel vibration, pressure, and light touch, proprioception and nerve conduction amplitude and velocity tests (assessed via nerve conduction studies) also provide objective information about large nerve fiber function [15, 18, 37, 38]. However, nerve conduction studies are not recommended for routine VIPN monitoring in children because the testing is painful. Pin-prick sensation testing is an objective assessment method that is sometimes used to evaluate small fiber function, but the testing procedure is time-consuming and uncomfortable. As an alternative, testing the child's temperature sensibility-the ability to detect "cold" when a cold object, such as a metal tuning fork, is placed on the skin-is an efficient and non-painful objective approach for assessing small fiber function.

Regarding composite measures, the results of two studies provide evidence that the pediatric modified-Total Neuropathy Scale© (peds-mTNS©) has strong psychometric properties [16, 31]. The peds-mTNS© was modified from the original Total Neuropathy Scale© (TNS©)-a composite measure that has been extensively tested in adult oncology populations and found to be reliable, valid, sensitive and responsive. [32, 35, 39-42]. The peds-mTNS© has three items that quantify subjective sensory, motor, and autonomic symptom severity. This tool also provides a rubric for scoring several objective VIPN measures (light touch, pin and vibration sensation, strength, and deep tendon reflexes). The ped-mTNS© has been shown to be reliable when used to measure VIPN in children ages 5-18 (Cronbach's α = 0.76; inter-rater and intra-rater reliability correlations >0.9) [31]. The measure is also valid based on its ability to discriminate between control subjects and those with cancer (P<0.001), and demonstrates statistically significant score correlations with balance (spearman correlation (r_s) = -0.626; P<0.001) and manual dexterity measures (r_s = -0.461; P<0.001). Furthermore, it can detect

Table 1. Objective Peripheral Neuropathy Assessment Approaches for Use in Children [14, 38, 99]

Test	Nerve Fiber Evaluated	Procedure	Advantages	Disadvantages
Deep Tendon Reflexes	Large	Reflexes are graded on a scale from 0 (normal) to 4 (all reflexes absent). Test using a reflex hammer with the child's limbs relaxed. Test bilateral Achilles, patellar, brachioradialis, bicep, and tricep tendon reflexes.	The test can be conducted quickly and with children <5 years of age.	Some children may elicit a "fake" reflex response by moving their leg or ankle on their own. The child may have trouble sitting still and relaxed during the test. Requires clinician training and practice to increase testing accuracy.
Strength	Large	Strength is scored from 0 (normal) to 4 (paralysis). While sitting on an exam table or on the edge of the bed, the child is asked to: • Curl their toes downward and resist clinician attempts to uncurl their toes. • Flex the foot upwards and resist clinician attempts to push the foot down. • Push down on the clinician's hand with their foot as if the hand is a gas/brake pedal, and resist clinician attempts to push the foot up. • Raise the leg (with knee bent) and resist clinician attempts to push the leg down. • Make a fist and resist clinician attempts to bend their wrists while the clinician pushes up and down on the fist. • Grip two of the clinician's fingers with their hands and resist clinician attempts to pull their fingers out of the child's grip. • Flex both arms/biceps and to resist clinician attempts to extend (un-flex) the arms. • Hold both arms out to the side (like wings) and resist clinician attempts to push the arms back down to the child's sides.	The child may enjoy proving his/her strength.	It may be difficult for the clinician to objectively score diminished strength. The test is time-consuming and difficult to conduct in very young children.
Vibration sensation	Large	Strike a 128 Hz tuning fork with the palm of the hand and place the tip to the bony surface of the great toe bilaterally. Ask the child tell when the "buzzing" or "vibration" has stopped. Perform this test bilaterally and move from distal to proximal areas if no vibration is felt.	The test requires minimal clinician training. Children enjoy the testing.	The test requires that children be continually refocused on the vibration sensation. Young children may not be able to communicate precisely when the vibration stops.
Semmes-Weinstein Monofilaments (Pressure)	Large	Ask the child to close their eyes. Place the smallest filament at different locations on each hand and foot for a couple seconds each time. Ask the child to state when they feel the filament touch their skin. Vary the sites and speed of the test so that the child cannot predict the next location. If the child cannot detect the smallest filament after two attempts, the next-largest filament is used.	Objective measure that can evaluate large nerve fiber function.	The test is time-consuming, difficult to conduct in very young children, and requires specialized equipment (monofilaments) and clinician training.
Touch	Large	With the child's eyes closed, brush a cotton ball across the skin in different areas on all extremities. Ask the child to state whether they can feel the cotton ball and where it is being applied. Perform this test bilaterally and move from distal to proximal areas if sensation is reduced.	A non-painful measure of large nerve fiber function. Children enjoy the testing.	The test is time-consuming.
Proprioception	Large	These tests evaluate balance and coordination. Tests that can be used include the finger-to-nose test, thumb-to-finger test, up/down test, and the Romberg test.	A non-painful measure that can evaluate large nerve fiber function. Children enjoy the testing.	It may be difficult to explain the procedure to a child.
Nerve Conduction Studies	Large	Evaluates nerve impulse transmission following electrical stimuli.	Can provide objective information about nerve conduction amplitude and velocity.	The tests are expensive, inconvenient (requires a neurologist referral), and uncomfortable for the child.
Pin-prick Sensation	Small	Ask the child to describe what if feels like when a sharp object (e.g. pin, neuro-tip) is placed on their skin. Perform this test on all extremities. The sensation should be one of pain rather than pressure. Perform this test bilaterally and move from distal to proximal areas if sensation is reduced.	An objective measure that can evaluate small fiber function.	The test is time-consuming and uncomfortable for the child.
Temperature sensation	Small	Use a cool object, such as a metal tuning fork, and place on the child's skin, ask if they feel it as "cold". Perform this test bilaterally and move from distal to proximal areas if sensation is reduced.	The test is quick and easy to conduct and not painful for the child.	It may be difficult for young children to differentiate variations in temperature sensation.

Note. Modified from "Evaluation and Management of Peripheral Neuropathy in Diabetic Patients With Cancer", by C. Visovsky, R.R. Meyer, J. Roller, and M. Poppas, 2008, *Clinical Journal of Oncology Nursing, 12,* p. 245. doi:10.1188/08. CJON.243-247. Copyright 2008 by Oncology Nursing Society. Adapted with permission.

Table 2. Treatment- and Patient-related Predictors of Vincristine-Induced Neuropathy in Pediatric Patients

Category	Predictor	Supporting Evidence	Vincristine Treatment Recommendations	References
Treatment-Related Factors	Higher Dose	Stronger evidence in adults but less established in pediatrics	Maximum 2 mg dose	[52]
	Higher drug concentration	Stronger evidence in adults but less established in pediatrics	None	[54, 55]
	Concomitant Azole Antifungals	Many case reports and some epidemiological studies	Avoid concomitant use	[56-58]
Patient-Related Factors	Race	Higher occurrence in Caucasians than African-Americans in analyses of clinical trials	None	[60, 61]
	Age	Higher occurrence in older children and adults in analyses of clinical trials	None	[60, 64]
	Charcot-Marie-Tooth Disease	Many case reports and some epidemiological studies	Contraindicated	[70-72]
	Guillain-Barre Syndrome	Some case reports	None	[74, 75, 100]
	Patient genetics	Significant hits from candidate (*CYP3A5*3*) and genome-wide (*CEP72*) pharmacogenetic studies	None	[60, 76]

subtle differences in VIPN severity as demonstrated by its lack of floor and ceiling effects [31].

The revised Total Neuropathy Score©-Pediatric Vincristine (TNS©-PV) is another TNS© variant that has been tested for use in children receiving vincristine [30]. The 5-item TNS©-PV quantifies subjective numbness, tingling, and neuropathic pain. Objective assessments are used to quantify vibration sensibility and deep tendon reflexes. This tool is valid for use in pediatric populations receiving vincristine based on moderately strong and statistically significant score correlations with cumulative vincristine dosage (r = 0.53; P<0.01), pharmacokinetic parameters (r = 0.41; P<0.05), and the NCI-CTCAE and Balis grading scale scores (r = 0.46-0.52; P<0.01). Additionally, the TNS©-PV is internally reliable (Cronbach's α = 0.84), responsive to change over time, and feasible for use in children ≥6 years of age. When compared with the ped-mTNS©, the TNS©-PV is more abbreviated. With practice, clinicians can complete the TNS©-PV assessment in five to ten minutes, depending on the child's ability to cooperate.

In addition to objective assessment, it is also important to ask children and/or their caregivers to provide subjective ratings of VIPN symptom severity. Subjective ratings provide information about both small and large nerve fiber function, and inform clinicians about the patient's perceptions of numbness, tingling, neuropathic pain in the upper and lower extremities, jaw pain, hoarseness, and constipation. Functional tests can be used to assess ankle range of motion [43], balance [44], lower extremity and grip strength [43], gross and fine motor development [43, 45, 46] and overall fitness [43]. Questionnaires can be used to assess painful VIPN [30, 47] and effects on QOL [43]. Valid and reliable measures should also be used to evaluate VIPN-associated psychological sequela and cognitive impairment in long-term pediatric cancer survivors. However, it is important to note that many tests and questionnaires used to quantify VIPN-associated outcomes have not been comprehensively validated in pediatric oncology populations. Moreover, complex motor function and fitness tests, although used as outcomes measures in research studies, are impractical for monitoring VIPN in clinical settings due to the time, staff training, and equipment needed to conduct the testing.

In conclusion, it is important that pediatric clinicians monitor the short- and long-term consequences of vincristine treatment. Psychometrically strong and clinically feasible VIPN assessment tools, such as the TNS©-PV, are useful for quantifying VIPN signs and symptoms. However, other types of validated neuropathy assessment tools are still needed to assess long-term VIPN-associated outcomes such as pain and psychological symptoms, functional and cognitive disability, and impaired QOL. Lastly, given that routine VIPN assessment does not always occur in busy clinical settings, future research is needed to address VIPN assessment implementation barriers and to identify the best approach for translating evidence-based VIPN assessment approaches into practice.

Risk factors for VIPN

Treatment-related factors

Some treatment-related risk factors have been reported to partially explain the heterogeneous onset and severity of VIPN (**Table 2**). It is well established in adults that peripheral neuropathy, across drug-related causes, is a cumulative toxicity that increases with continued treatment [48]. Higher single doses increase the occurrence of VIPN early in therapy [49] and throughout treatment [50], thus providing the rationale for a maximum vincristine dose of 2 mg [51]. However, the effect of dose is less well established in pediatric patients, in whom cumulative vincristine dose does not appear to be associated with motor neuropathy severity [52]. Similarly, greater vincristine drug concentrations, or pharmacokinetics, have been associated with increased neuropathy in adults [53] but not pediatric patients [54, 55].

Despite the lack of direct evidence of an association between drug concentration and peripheral neuropathy, particularly in pediatric patients, there is strong evidence that concomitant treatment with interacting medications, particularly azole antifungals, increases VIPN. A review of case reports identified 47 cases of patients treated concomitantly with azole antifungals (itraconazole, ketoconazole, posaconazole, voriconazole) who experienced vincristine toxicity [56]. Direct comparisons of pediatric patients found that during concomitant treatment there is an increase in vincristine-induced toxicity [57, 58]. Though no pharmacokinetic data is available, the assumed mechanism for this interaction is inhibition of CYP3A by azole antifungals, leading to increased vincristine concentrations and enhanced VIPN. Further support for this mechanism is provided by the differences in toxicity occurrence and severity across azoles, with relatively small increases in toxicity seen with fluconazole, a weaker CYP3A inhibitor than the other azoles. An increase in VIPN in patients receiving concomitant aprepitant, another CYP3A4 inhibitor, further supports this mechanism [49]. However, it is possible that the azole antifungals themselves are neurotoxic and that the interaction is due to additive toxicity, not a pharmacokinetic interaction. Indeed, peripheral neuropathy has been reported in patients receiving long-term antifungal treatment in the absence of neuropathic chemotherapy, with the relative occurrence of neuropathy across antifungals similar to the patterns identified in the drug interaction studies [59]. Regardless of the mechanism, given the many case reports and comparative analyses, concomitant treatment with CYP3A4 inhibitors, particularly the azole antifungals, should be avoided in patients receiving vincristine treatment.

Patient-related factors

There is a great deal of interest in discovering patient-specific predictors of VIPN to guide individualized treatment that optimizes therapeutic outcomes. Several studies have reported that Caucasian patients have greater incidence and severity of VIPN than African-American patients [60, 61]. This is particularly interesting given the opposite association with race has been reported for paclitaxel-induced peripheral neuropathy [62, 63]. Increased age has also been associated with increased risk of VIPN in adult [49] and pediatric [14, 60, 64] patients. This is unlikely to be due to vincristine pharmacokinetics [54, 65], as drug concentrations are lower in older children than younger children due to the 2 mg dosing limit [66]. Finally, though deficiencies in vitamin B12 and other micronutrients are associated with neurotoxicity in the general population [67], vitamin levels are not meaningfully different in patients who do and do not experience VIPN [68].

There is overwhelming evidence that patients with the hereditary neuropathy condition Charcot-Marie-Tooth (CMT) Disease are highly sensitive to VIPN. Retrospective testing of patients who developed severe neuropathy during vincristine treatment have found high rates of CMT [69] and many case reports have been published in the literature [70-72]. A family history of CMT should be considered a contraindication to vincristine treatment. Treatment substitution with the pharmacologically similar, but possibly less neurotoxic, vindesine has been reported to be successful [73]. Although there are fewer case reports, a very severe peripheral neuropathy leading to quadriparesis has been reported in patients with Guillain-Barre Syndrome treated with vincristine [74, 75].

Aside from the strong genetic effect of CMT, there is particular interest in discovering com-

Table 3. Pharmacogenetic Associations with Vincristine-Induced Neuropathy in Pediatric Cancer Patients

Reference	N	Age	Location and Race	Cancer Type	Vincristine Dose and Schedule	Genes and SNPs Analyzed	Neuropathy Phenotype	Pharmacogenetic Associations
Hartman Leukemia Research 2010 [79]	34	4-12	Netherlands	ALL	2.0 mg/m^2 × 31-34 cycles	CYP3A5*3, ABCB1*2, MAPT haplotype	Percentile score on Movement Assessment of Battery for Children 1 year after treatment completion	No associations
Egbelakin Pediatric Blood Cancer 2011 [76]	107	1-18	United States, 98% Caucasian	preB ALL	1.5 mg/m^2 weekly followed by a year of maintenance	CYP3A5*3	Grade of neuropathy	CYP3A5*3 (non-expresser) had greater neuropathy occurrence and severity
Guilhaumou Cancer Chemotherapy and Pharmacology 2011 [64]	26	2-16	France	Various	1.5 mg/m^2 weekly × 3 cycles	CYP3A4*1B, CYP3A5*3, ABCB1*2	3+ Global Toxicity Score (sum of pain, peripheral neuropathy, and GI toxicity grades)	No associations
Diouf Jama 2015 [60]	321	0-19	United States, 65% Genetically European	ALL	1.5 or 2.0 mg/m^2 weekly followed by a year of maintenance	1,091,393 SNPs imputed from genome-wide association	Grade 2-4 peripheral neuropathy	CEP72 (rs924607) associated with increased neuropathy risk and severity
Gutierrez-Camino Pharmacogenetics and Genomics 2015 [81]	142	NR	Spain	B-ALL	1.5 mg/m^2 weekly × 4 cycles	CEP72 (rs924607)	Grade 2+ peripheral neuropathy	No association
Ceppi Pharmacogenomics 2015 [78]	320	NR	Canada, 98% French-Canadian	ALL	1.5 mg/m^2 weekly × 4 doses followed by 2 mg/m^2 Q3W for 100 weeks	17 SNPs in TUBB1, MAP4, ACTG1, CAPG, ABCB1, CYP3A5	Grade 1-2 or 3-4 peripheral neuropathy	Hypothesis generating associations with ACTG1, CAPG, and ABCB1

Abbreviations: ALL: Acute lymphoblastic leukemia, NR: Not Reported, SNP: Single nucleotide polymorphism.

mon genetic polymorphisms that are predictive of VIPN (**Table 3**). Based on the importance of CYP3A5 in vincristine metabolism, Egbelakin et al. conducted a pharmacogenetic-pharmacokinetic-VIPN analysis focusing on the non-expresser *CYP3A5*3* (rs776746) genotype [76]. In 107 pediatric ALL patients there was an increase in VIPN occurrence, severity, and duration, and more dose reductions and omissions in patients who were homozygous for *CYP3A5*3*. Patients who expressed CYP3A5 also had greater metabolite levels 1-hour after dosing, and there was a significant inverse association between metabolite levels and neuropathy severity. This provides compelling evidence that decreased vincristine metabolism in CYP3A5 non-expresser patients increases VIPN (**Figure 1**). This would also explain the inter-race difference in VIPN mentioned earlier, as the proportion of African Americans who expressCYP3A5isfarhigherthanCaucasians(approximately 60% vs. 20%) [77]. However, as with other candidate pharmacogenetic associations, successful replication has been extremely challenging. Multiple independent studies in pediatric patients have not identified associations between *CYP3A5*3* and drug concentrations [65] or VIPN [64, 78, 79].

Several studies have also analyzed SNPs in *ABCB1*, the gene that encodes for the highly promiscuous p-glycoprotein transporter responsible for efflux of many cancer agents. There are three polymorphisms in *ABCB1* (1236C>T, 2677G>T(A), 3435C>T) that comprise the *2 haplotype. These polymorphisms have been reported, but not validated, to be associated with many treatment-related outcomes in cancer patients. Individual studies have reported marginal decreases in vincristine elimination [80] while others have found no association with pharmacokinetics [65] or VIPN [64, 65, 78, 79]. Alternatively, a nominal association was reported for a different SNP in the *ABCB1* promoter (rs4728709) for which there was evidence of a protective effect, and two other SNPs in *ACTG1* (rs1135989) and *CAPG* (rs-2229668, rs3770102). However, these initial discoveries in a single retrospective analysis without appropriate statistical correction should be viewed skeptically until successful independent replication is reported [78].

In addition to these candidate gene approaches, Diouf et al. recently reported results of a genome-wide association study of VIPN in 321 pediatric patients receiving long-term continuation treatment for ALL on prospective clinical trials [60]. Analysis of more than 500,000 SNPs identified a single SNP in the promoter region of *CEP72* that increased VIPN occurrence and decreased the cumulative dose at VIPN onset. The investigators provided mechanistic support for this finding by verifying that the promoter SNP decreases *CEP72* expression, and that decreased *CEP72* expression increases neuronal cell sensitivity to vincristine in vitro. Interestingly, this variant is less common in African-American (Minor Allele Frequency = 10%) than Caucasian (MAF = 40%) individuals, providing a second plausible explanation for the inter-race difference in VIPN. Despite the well-conducted pharmacogenetic analysis and intriguing mechanistic work, this finding also requires independent replication prior to prospective clinical translation. One initial attempt did not detect any association with VIPN in 142 pediatric patients receiving induction therapy for B-cell ALL [81], perhaps due to the different treatment settings.

Prevention & treatment

Multiple trials, primarily in adults, have sought to determine if medications can be given concomitantly with chemotherapy to prevent and/or treat VIPN. Unfortunately, the result of these efforts have been largely disappointing. The majority of trials suffered from limitations such as insufficient sample size or power, high dropout rate, variation in primary outcomes limiting comparability, and early trial termination [82]. Additionally, these trials occurred in a variety of treatment settings with various chemotherapy regimens, including combinations with other neuropathic agents, making interpretation and extrapolation a major challenge. The American Society of Clinical Oncology published a clinical practice guideline in 2014 reviewing the available literature, their bottom line recommendation was that no agent currently demonstrated consistent evidence to prevent chemotherapy-induced peripheral neuropathy (CIPN). Regarding interventions for established CIPN, duloxetine is the only drug with demonstrated efficacy for paclitaxel-or oxaliplatin-induced painful CIPN [82].

Specifically, agents such as venlafaxine, amifostine, glutamine, amitriptyline, Org 2766, ele-
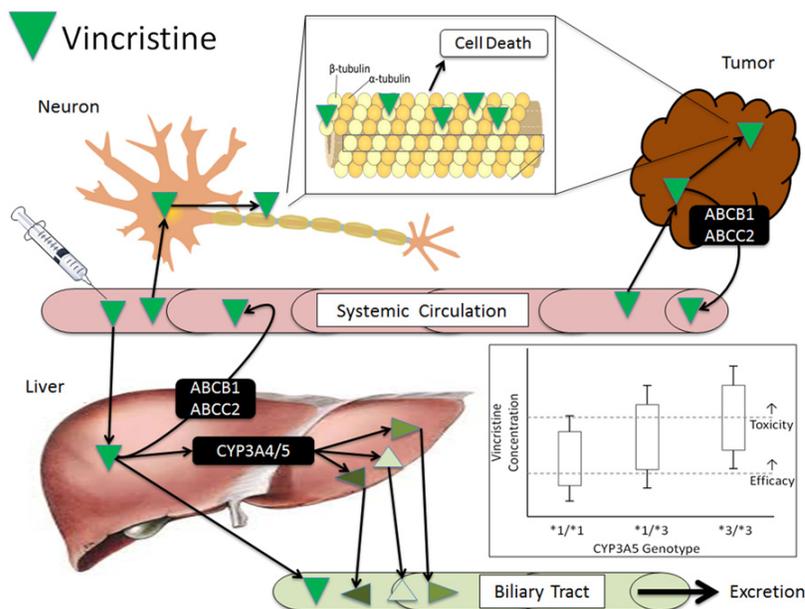
Figure 1. Vincristine pharmacokinetics and pharmacodynamics. Vincristine enters the systemic circulation through direct intravenous administration. It is distributed via passive diffusion into organs for metabolism (liver), efficacy (tumor) and toxicity (neuronal cells). Vincristine is a substrate of several efflux transporters including ABCB1 (P-gp) and ABCC2, ABCC3, and ABCC10, which return vincristine to the circulation. In the tumor and neuron vincristine binds to the β subunit of tubulin, causing cellular apoptosis. In the liver vincristine is partially metabolized by CYP3A4 and CYP3A5 to three inactive metabolites, followed by biliary excretion. The inset box and whisker plot is a hypothetical representation of relative systemic vincristine concentrations in patients stratified by their CYP3A5*3 (non-expresser) status. Patients heterozygous (*1/*3) or homozygous (*3/*3) for the non-expresser genotype would have greater systemic concentrations, causing more of these patients to have toxic levels of vincristine.

ctrolytes and vitamins were studied for CIPN prevention. Out of these, only amitriptyline and Org 2766 were looked at in patients receiving vinca alkaloids. Amitriptyline was evaluated in a double-blind, placebo-controlled trial of 114 patients who were initiating therapy with a vinca, platinum, or taxane. There was no difference in neuropathic symptoms between groups and dry mouth and tremor were more severe in the amitriptyline cohort [83]. Org 2766 is a synthetic ACTH compound that has been shown to modulate VIPN in a snail model; however in a placebo-controlled clinical trial of 150 vincristine-treated patients, no difference was reported in neuropathy-free interval between treatment groups [84, 85]. Venlafaxine and amifostine have both been independently studied for their ability to prevent platinum-induced peripheral neuropathy. Although beneficial effects have been recorded for both agents, more investigation is needed to verify that either is effective for preventing VIPN [86-91].

Similarly, demonstration of effectiveness in the treatment of existing neuropathy has been extremely challenging. Duloxetine has shown the most promise for the treatment of CIPN, demonstrating reduced pain scores compared to placebo in a randomized, double-blind, placebo-controlled cross-over study of 231 patients, however vincas were not included in this trial [92]. Gabapentin, an agent frequently given adjunctively to treat CIPN, was studied in a randomized, multicenter, double-blind, placebo-controlled crossover study in 115 patients receiving vincas, platinums and taxanes. Symptom severity was similar between the patients who received gabapentin versus placebo and therefore this trial failed to demonstrate a benefit to the addition of gabapentin [93]. The proposed mechanism for efficacy of gabapentin in CIPN is related to its binding to the alpha-2-delta type-1 ($\alpha_2\delta$-1) subunit of voltage-gated calcium channels, which displays increased expression in certain peripheral neuropathy models [94]. Interestingly, in animal models, exposure to vincristine did not affect the level of $\alpha_2\delta$-1 mRNA in either the dorsal spinal cord or the dorsal root ganglia, although paclitaxel and oxaliplatin did. In this study, paclitaxel and oxaliplatin-induced mechanical allodynia was responsive to oral doses of gabapentin, whereas vincristine-induced peripheral neuropathy was not [95], possibly explaining the results seen in the randomized controlled trial in humans. Finally, lamotrigine was also shown not to be beneficial in patients receiving chemotherapy [96].

More recently, clinicians have looked to alternative therapies to prevent and treat CIPN. In a randomized, double-blind, placebo-controlled

trial of 208 patients receiving multiple neurotoxic chemotherapy agents including vinca alkaloids, platinums, taxanes or thalidomide a topical compounded preparation containing amitriptyline, ketamine and baclofen was shown to improve CIPN symptoms. Patients identified decreased tingling, cramping, and burning pain of the hands as well as improvement in the patients' ability to hold a pen and write [97]. Similar trials of topical menthol and capsaicin are ongoing [82]. Finally, there is some evidence that physical therapy improves ankle and knee strength as well as range of motion in children with ALL [98]. Despite the widespread interest and numbers of clinical trials looking to prevent and treat chemotherapy-induced neuropathy, no clear standard has been determined or can be recommended at this time.

Conclusion

In summary, vincristine is an antineoplastic agent that is widely incorporated into multi-agent chemotherapy regimens to treat a variety of malignancies. Dose-limiting sensorimotor neuropathy presents a challenge to clinicians, particularly in the treatment of pediatric patients. Reliable and sensitive composite measures for detecting VIPN onset and progression in pediatric patients have been developed and validated, but are not uniformly integrated into clinical practice. Despite avoidance of vincristine administration concomitantly with interacting drugs, and in patients with genetic predispositions to neuropathic conditions, a large number of patients still develop VIPN. Pharmacogenetic associations with VIPN risk have been reported, however, few of the promising candidates have been successfully replicated and none have been translated into clinical practice. Although a variety of agents have been studied for VIPN prevention and/or treatment, they have not been proven effective. Moving forward, it is critical that VIPN measurement is standardized so that studies can be conducted to identify high-risk patients and to evaluate novel preventative and therapeutic approaches.

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Disclosure of conflict of interest

None.

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