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Peripheral neuropathy in children and adolescents treated for cancer

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Summary

Peripheral neuropathy is a well-recognized treatment-related toxicity among children with cancer and is associated with exposure to neurotoxic chemotherapy agents. Acute damage, may manifest in sensory, motor, and/or autonomic neurons with symptoms that are rarely life threatening, but often severe enough to interfere with function during therapy and after treatment ends. The type of

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neuropathy, and specific symptoms, are associated with multiple factors, including age at time of therapy, genetic predisposition, chemotherapy type, and cumulative dose, and exposure to other agents during therapy. The aims of this review are to describe the peripheral neuropathy phenotype, among both children during cancer therapy and among survivors, to summarize host/genetic and treatment related risk factors for neuropathy, and to outline strategies to monitor and detect neuropathy during and after therapy. In addition, strategies for medical management of neuropathy during treatment are discussed and potential rehabilitation interventions to prevent or remediate functional loss are proposed.

Introduction

Modern therapy has improved survival for children with cancer;¹ however, treatment has unintended consequences. These toxicities may interfere both with optimal delivery of treatment as well as daily function and quality of life. Once thought to be transient, peripheral neuropathy is a well-recognized treatment-related toxicity among children with cancer and is associated with exposure to neurotoxic chemotherapy, including vinca alkaloids and platinum compounds. Acute neuropathy is reported among 20-60% of children with acute lymphoblastic leukemia (ALL),^{2,3} and up to 85% of children with lymphoma and non-central nervous system (CNS) solid tumors.⁴ Estimates of treatment-induced neuropathy among children with CNS tumors, however, are lacking, despite common exposure to both vinca alkaloids and platinum compounds.

Exposure to neurotoxic agents during childhood cancer therapy causes acute damage, which may manifest in sensory, motor, and/or autonomic neurons.⁵⁻⁸ Symptoms, including dampening or loss of peripheral reflexes, pain, numbness, tingling, weakness, difficulty swallowing, altered thermoregulation, poor blood pressure control, and problems with intestinal motility, are rarely life threatening; however, they are often severe enough to interfere with function during and after completion of therapy.⁹ Symptoms of peripheral neuropathy usually start distally and may or may not progress proximally. They also may disappear when the offending agents are withdrawn. However, the type of neuropathy, proximal progression, and extent and persistence of symptoms in survivors after completion of therapy are associated with multiple factors, including genetic predisposition, chemotherapy type, chemotherapy cumulative dose, age at time of exposure, and exposure to other agents during therapy. Persistence into survivorship is particularly concerning due to the associated impact on function and quality of life and affects survivors across multiple tumor types. In acute lymphoblastic leukemia (ALL) survivors, long-term loss of protective sensation, vibratory detection, ankle range of motion, and distal lower extremity strength have been documented, and are associated with postural control deficits and limited walking efficiency.¹⁰ Among adult survivors of childhood onset extracranial solid tumors, 20% experience cisplatin-related sensory loss, and nearly 18% experience vincristine-associated motor neuropathy.¹¹ Little is known about the contributions of therapy to neuropathy in adult survivors of central nervous system (CNS) tumors, as it remains a challenge to decipher whether neuropathy is secondary to tumor location, surgery, or treatment factors. However, neuropathies, secondary to treatment exposures, are common among adult

survivors of childhood cancer and may be amenable to ongoing rehabilitation to improve function.

The aims of this review are to describe the peripheral neuropathy phenotype among children during cancer therapy and in survivors who have completed therapy, to summarize host/genetic and treatment related risk factors for neuropathy, and to outline strategies to monitor and detect neuropathy. In addition, we discuss strategies for medical management of neuropathy during and after treatment, and propose potential rehabilitation interventions to prevent or remediate functional loss.

Search strategy and selection criteria

Relevant peer-reviewed literature was identified by querying PubMed with the search terms “peripheral neuropathy”, “peripheral neurotoxicity”, “chemotherapy induced peripheral neuropathy”, “childhood cancer”, “leukemia”, “solid tumor”, “survivorship”, “vinca alkaloids”, “platinum”, “genetic”, “quality of life”, and “performance” from 1990–2018. Articles were also selected from authors’ personal files; and from reference lists of identified papers. Only articles in English were included. Article selection was based on relevance to the present review.

Peripheral neuropathy

Acute neuropathy presents as a single, or a combination of, motor, sensory and/or autonomic impairments (Table 1).¹² Motor neuropathy can be symmetrical or asymmetrical and occurs primarily with vinca alkaloid administration. Motor neuropathy is manifested as muscle weakness, muscle atrophy, cramping, uncontrolled muscle twitching, and gradual decrement and/or loss of peripheral deep tendon reflexes.¹² Loss of ankle dorsiflexion range of motion and lower extremity weakness often present as foot drop (loss of eccentric control of the ankle dorsiflexor musculature), accompanied by loss of the longitudinal arch of the foot and a characteristic “foot slapping” while walking.^{13,14} These changes may be best appreciated after a minute or two of walking, or when the child ascends or descends stairs. In young children, gross motor developmental milestones, for example walking, running, climbing and jumping may be significantly delayed. In the upper extremity, weakness presents as difficulty with eye-hand coordination, problems grasping small objects, difficulties with pencil grip, and difficulty with daily self-care activities such as buttoning a shirt or tying shoes.¹⁵ Sensory changes typically begin distally, manifest symmetrically, have a “glove and stocking” distribution,” starting in the fingers and toes, and moving proximally to the hands and feet.¹⁶ Children often report paresthesias (e.g. burning, tingling, or pain), numbness, temperature intolerance, or exaggerated discomfort to a stimulus resulting in less use of the affected extremities or body parts.¹³ Vincristine exposure is associated with jaw pain that can affect chewing;¹⁷ however, this symptom is usually observed with the first administration of the agent and is typically transient. Decreased somatosensory input, compounded by decreased motor strength and flexibility, contributes to increased risk of balance problems in affected children.¹⁸ Autonomic dysfunction, caused by chemotherapy exposure, can present as orthostatic hypotension, and gastrointestinal disturbances, including constipation or watery diarrhea.¹⁹

Once present, neuropathy may persist in children with cancer during therapy because of continued exposure to neurotoxic agents, and may continue long-term post-therapy if there was more permanent nerve damage. In a study of 128 children with ALL treated according to Children's Oncology Group (COG) protocols after 2004, 78% developed peripheral neuropathy that persisted throughout the first year of treatment, even with reductions in vincristine dose intensity.⁸ Progression of symptom severity after treatment is completed, or "coasting", is also possible, and has been reported with vincristine, platinum, bortezomib, and thalidomide exposures.^{19,20} Permanent damage to peripheral nervous system structure and function impacts fine motor skills, balance, mobility, endurance and potentially, quality of life.^{5,6,10,11,18,21,22} Reinders-Messilink et al report impaired upper extremity movement fluency and difficulty with handwriting among 18 ALL survivors 2 years after treatment when compared to healthy controls;²¹ and Galea et al report increased postural sway and velocity during static tandem standing with eyes closed among 32% of 79 ALL survivors (a median of 5 years off therapy), compared to only 2% of 83 age-matched controls.²³ In adult survivors of childhood ALL (N=415), impaired dorsiflexion range of motion (<5 degrees) as a result of vincristine exposure is associated with a nearly 4-fold (OR 3.9; 95% CI 2.4–6.3) increase in risk for poor performance on the 6-minute walk test;¹⁰ and, in adult survivors of non-CNS solid tumors (N=531), cisplatin induced sensory impairment is associated with reduced mobility (OR 2.0; 95% CI 1.0–4.0), and with poor performance on the 6-minute walk test (OR 1.7; 95% CI 1.0–2.8).¹¹ In a cohort of adult survivors of childhood cancer (N=1,667, median 25.5 ± 7.8 years from diagnosis), presence of persistent sensory symptoms is associated with significantly reduced physical and mental quality of life as measured by the medical outcomes survey short-form 36 (SF-36), indicating a reduction in self-reported health-related quality of life.²⁴

Chemotherapy agents/mechanism of injury

Chemotherapy agents associated with peripheral neuropathy in the pediatric population act upon multiple sites in the nervous system (Figure 1) and may be grouped according to their action upon microtubules: (1) microtubule-targeting drugs, (2) microtubule stabilizing agents (MTSAs), and (3) non-microtubule-active drugs (Table 2). Microtubule-targeting drugs bind to one of three main classes of sites on tubulin, the vinca alkaloid domain, the paclitaxel site, and the colchicine domain (the colchicine domain will not be further discussed in this review, as drugs targeting this domain have not been utilized to treat pediatric neoplasms due to other toxicities).²⁵ Non-microtubule-active drugs act elsewhere upon the peripheral nervous system. Chemotherapeutic regimens may use more than one agent from each class, or across classes. This makes it difficult to determine which agent, or agents, are responsible for the signs and symptoms of neuropathy experienced by a particular patient. Unfortunately, additive effects are possible.

Vinca domain microtubule targeting drugs include the vinca alkaloid class of agents and include vincristine, vinblastine, vindesine and vinorelbine. Vinca alkaloids bind to the β -subunit of tubulin heterodimers, preventing their polymerization and incorporation into microtubules, causing cytoskeletal disorganization and microtubule disorientation within axons.^{26,27} Disorganization and disorientation of microtubules leads to inhibition of vesicle-mediated transport of neurotransmitters within the axoplasm and potentially axonal

degeneration and denervation or “dying back neuropathy”. Vincristine, the most common agent associated with peripheral neuropathy among children with cancer, is an essential component of treatment for ALL, lymphoma, neuroblastoma, Wilms tumor, rhabdomyosarcoma, Ewing sarcoma, medulloblastoma, low-grade glioma and retinoblastoma. Vincristine exerts its cytotoxic effects by interfering with microtubule formation and mitotic spindle dynamics, leading to mitotic arrest and cell death.²⁵ Electrophysiological testing done in children during vincristine treatment demonstrates minor changes in axonal conduction velocity but notable reductions in compound muscle action potentials (CMAPs) (Table 3).^{28,29} One study also noted reductions in upper extremity sensory conduction velocities and sensory nerve action potentials.²⁹ These changes are consistent with a “dying back” neuropathy. Depending on the vincristine dose and schedule of administration, motor and/or sensory neuropathy (grade 2+) occurs in approximately 25% of patients.²⁶ This nerve damage can persist, with motor changes notable on electrodiagnostic testing being more common than sensory abnormalities (Table 3).

Despite its structural similarity to vincristine, differing by the substitution of a methyl group for the formyl group on the vindoline nucleus, vinblastine, a frequent component of pediatric chemotherapy regimens for Hodgkin disease, desmoid tumors and low-grade gliomas, is less likely to result in peripheral neuropathy than vincristine.³³ Vindesine is not commonly used in pediatric protocols, though it has a neurotoxicity profile similar to that of vincristine.³⁴ Vinorelbine, primarily used to treat non-small cell lung cancer among adults, has been used in protocols for children with relapsed or refractory leukemia, Hodgkin lymphoma, sarcomas, and brain tumors.^{35–39} Rates of neuropathy after vinorelbine exposure range from 3%, when delivered in conjunction with cyclophosphamide for refractory solid tumors,³⁷ to 24% when delivered subsequent to another neurotoxic agent, bortezomib.⁴⁰

MTSAs (paclitaxel and docetaxel) are often used to treat adult malignancies, including ovarian cancer, breast cancer, head and neck cancer, lung cancer, Kaposi sarcoma, cervical cancer, and pancreatic cancer, but are rarely utilized in the treatment of pediatric cancer. MTSAs cause a primary sensory neuropathy. Preclinical work has demonstrated that MTSAs induce swollen and vacuolated mitochondria in both myelinated axons and C-fibers in peripheral sensory nerves, which correlates with MTSA-induced peripheral neuropathy.⁴¹ In animal models, MTSAs also block fast axonal transport and induces microtubule aggregation without degenerative changes in peripheral nerves.^{42,43} However, this has not been confirmed in nerve biopsies from patients with MTSA-associated peripheral neuropathy.⁴⁴

Non-microtubule-active drugs include platinum agents (cisplatin, carboplatin, and oxaliplatin), and bortezomib. Platinum agents, primarily cisplatin and carboplatin, are used in treatment regimens for germ cell tumors, osteosarcoma, neuroblastoma, medulloblastoma, low-grade glioma, and retinoblastoma. Neuropathy among patients exposed to platinum compounds is a result of injury to the dorsal root ganglions (DRG),⁴⁵ where formation of intra-strand adducts and cross-links influence the structure of nuclear DNA and interfere with cell-cycle kinetics.^{46,47} Platinum also interacts with mitochondrial DNA, resulting in increased oxidative stress,⁴⁸ and activation of apoptotic pathways.^{49–52} Although DRG

neurons are post-mitotic, and non-dividing cells and DNA platination adducts are not lethal, the amount of DNA cross-links in DRG neurons at a given cumulative dose is significantly correlated with the degree of neurotoxicity.⁵³ Because the pharmacokinetics of carboplatin differs from that of cisplatin, prior studies have employed a 4:1 carboplatin to cisplatin dose equivalence adjustment in assessing associations of platinum compounds to neurotoxicity.¹¹ Most cases of platinum induced peripheral neuropathy occur after a threshold cumulative dose of 300 mg/m² is reached,⁵⁴ and almost all patients have objective evidence of nerve damage beyond a cumulative dose of 500-600 mg/m².⁵⁵ Because neuropathy following exposure to platinum agents is a result of injury to the DRG, neuropathy after platinum exposure is primarily sensory and electrophysiological evidence of reduced sensory nerve action potentials has been reported years after treatment (Table 3).^{31,56} Oxaliplatin, a third-generation platinum agent, also interacts with transcription factors and inhibits RNA polymerases, and is associated with immunogenic cell death.^{57,58} It is not commonly used in pediatric patients, primarily in the context of phase I and II trials. Oxaliplatin is associated with a cold-induced neuropathy, that does not occur with other platinum compounds.⁵⁹

Bortezomib, a 20S proteasome complex inhibitor, is approved for the treatment of myeloma and non-Hodgkin lymphoma and is currently being investigated for recurrent childhood leukemia and lymphoma. Bortezomib causes a primary sensory neuropathy which appears to be more common in adults than children.⁶⁰ Bortezomib leads to intracytoplasmic vacuolation, which is ascribed to mitochondrial and endoplasmic reticulum injury, and activation of the mitochondrial-based apoptotic pathway within DRG satellite cells.⁶¹

Genetic risk factors for peripheral neuropathy in children with cancer

Despite increasing knowledge regarding the mechanism of neurotoxic injury, there is a wide variation in the reported incidence, and symptom severity. Observations of inter-individual and ancestry-related differences in the prevalence of vincristine-induced neuropathy suggest that genetic variants may contribute to the incidence and/or severity of vincristine-induced neuropathy.⁶² However, initial studies designed to identify genetic variants were limited to a relatively small set of candidate genes known to be involved in vincristine pharmacokinetics. These studies did not yield reproducible findings, perhaps because they were limited in scope and did not use an agnostic approach.⁶² Candidate gene studies designed to identify genetic variants associated with cisplatin-induced peripheral neuropathy reported associations between the development of neuropathy during treatment and drug detoxification enzymes,^{63,64} as well as DNA repair genes;⁶⁵ similar to vincristine studies, these were not replicated in agnostic genome wide association studies (GWAS).⁶⁶

Recently, an agnostic GWAS approach using two different cohorts of children with ALL treated on St. Jude Children's Research Hospital or Children's Oncology Group protocols identified several single nucleotide polymorphisms (SNPs) associated with increased incidence of vincristine-induced neuropathy. The top SNP associated with an increased risk and severity of neuropathy (rs924607) resides in the promoter of the centrosomal protein 72 (*CEP72*) gene. The T allele is associated with a 2.7 fold increased risk of vincristine-induced neuropathy, and creates a binding site for the transcriptional repressor NKX6.3, which results in lower expression of CEP72, a centrosomal protein essential for microtubule

formation. Additionally, knockdown of *CEP72* increases the sensitivity to vincristine of both human induced pluripotent stem cell (iPSC) neurons and primary ALL cells from patients homozygous for the *CEP72* risk allele (T/T).² This association of the *CEP72* SNP with vincristine neuropathy, was validated in 2 additional adult cohorts of cancer patients.^{67,68} The most effective approach to mitigate chemotherapy-induced peripheral neuropathy has been dose reduction and/or discontinuation of therapy, which may ultimately decrease treatment efficacy. The identification of *CEP72* variant, characterized by increased sensitivity in both neurons and leukemia cells, offers the potential to reduce vincristine dose in susceptible individuals to decrease the risk of neuropathy, without compromising its therapeutic effect, if both neurons and leukemia cells are more sensitive to vincristine resulting in decreased efficacy. However, the sensitivity of leukemia cells to genetic variants has not yet been validated.

To date, there are no GWAS studies in pediatric populations. However, a GWAS with self-reported peripheral neuropathy symptoms (using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN twenty-item scale (EORTC QLQ-CIPN20)) as the outcome in a cohort of young adult cancer survivors identified Regulation Of Nuclear Pre-mRNA Domain-Containing Protein 1B (*RPRD1B*) using PrediXcan,^{66,69} a gene-based computational method which uses reference transcriptome (genotype-gene expression) data to generate models used to ‘impute’ gene expression levels from genotype data. An association between lower expressions of *RPRD1B* with cisplatin induced peripheral neuropathy was identified. Defects in *RPRD1B* expression inhibits DNA repair mechanisms critical in resolving cisplatin-induced injury,⁷⁰ and knockdown increases sensitivity to cisplatin.⁷¹

Challenges remain in the interpretation of genetic susceptibility studies. Comparison of results is difficult, due to differences in defining the neuropathy phenotype, and because not all studies control for covariates that can influence neuropathy (dose, duration of treatment, methods used to capture and quantitate the phenotype, etc.).⁷² Further studies are needed to understand how different gene variants predispose patients to vincristine, cisplatin- and other agent-induced neuropathy (as was done with *CEP72* SNP²), and to define the influence of rare variants of *CEP72* and other genes that will emerge from whole-exome and whole-genome sequencing.⁷³ Importantly, GWAS approaches, such as those that have been used in children exposed to vincristine, which are designed to examine the modifying impact of genetics on neuropathy among children with other neurotoxic exposures, are warranted. In addition, it is not known whether the same genetic variants that predispose to acute chemotherapy-induced neuropathy also predispose to persistent neuropathy, and the contribution of other genes to this phenotype, remains to be determined.

Other pre-existing genetic conditions may increase the risk for neurotoxicity secondary to cancer therapy. Reports of severe neuropathy after vincristine exposure have led to the discovery of undiagnosed, and at times asymptomatic, conditions in pediatric patients, such as Charcot-Marie-Tooth.⁷⁴ Neurofibromatoses may manifest with peripheral neuropathies and may be independent of tumor presence, as in neurofibromatosis 2.⁷⁵ Children with Down syndrome are at a higher risk for developing leukemia compared to other children, and as part of their phenotype, at baseline may have neurologic impairment, including

hypotonia. However, there is no information indicating an elevated risk of therapy induced peripheral neuropathy in children with Down syndrome. Further study in this population is warranted. Clinicians should consider both family history of neuropathy, and pre-existing neurological symptoms prior to initiation of neurotoxic therapy, and carefully monitor patients with histories or symptoms likely to be exacerbated by administration of neurotoxic agents.

Screening and evaluation

All children and adolescents receiving neurotoxic agents as part of their cancer therapy regimen should be screened by history and physical examination on an ongoing basis for signs and symptoms of peripheral neuropathy (Figure 2). Although some studies indicate an association between cumulative dose of neurotoxic agent and neuropathy,⁷⁶ others report associations with any dose,^{8,77} indicating that patients should be screened regardless of agent-specific dose received. Specific query is important as relying on unsolicited patient/family report is often insufficient to detect emerging neuropathies. One study, comparing documented patient report (medical record) to specific questions and objective testing in pediatric cancer patients, found that 40% of sensory neuropathy and 15% of motor neuropathy is unrecognized.⁷⁸ Optimal screening includes patient/parent interviews about changes in sensory, motor, or autonomic function, in conjunction with careful physical and neurologic exam. Signs and symptoms reflective of neuropathic pain, paresthesias and/or functional changes such as tripping while walking, regression of stair climbing ability, and difficulty with fine motor tasks may indicate emerging neuropathy and warrants further investigation.

Peripheral neuropathy is also associated with other patient factors, including age race and concomitant therapy. In patients with medulloblastoma treated in the second decade of life (10–20 years), over 70% of patients who received both chemotherapy and radiation experienced grade 2 neurotoxicity.⁷⁹ Compared to younger patients (>5 and <10 years), older patients (>10 years) experienced more neurotoxicity and ototoxicity while receiving cisplatin, lomustine and vincristine.⁷⁹ Measures of vincristine-induced peripheral neuropathy among 1539 patients with ALL, were positively associated with age, indicating worsening neuropathy.⁸ Race may also play a role in risk of chemotherapy-induced neuropathy. In children between one and 18 years of age with ALL, non-Hispanic White children had a significantly higher cumulative incidence of vincristine-related neuropathy during the first three years of therapy compared to Black, Hispanic, Asian or other children.⁸⁰ Children being treated for cancer are also at risk for other conditions, including fungal infection, and may also be receiving therapy with azole antifungals. Adverse interactions between azole antifungals and vincristine have been documented, due to shared metabolism through CYP3A4. Metabolic competition increases the length of vincristine exposure.⁸¹

Once screening has indicated a potential problem, clinical assessment of peripheral neuropathy in school-aged children and adolescents with neurotoxic exposure should be completed with validated measures to identify potential need for treatment modifications or rehabilitation intervention. Variants of the Total Neuropathy Score (TNS) adapted for pediatric use include the pediatric modified TNS (ped-mTNS) and the TNS-Pediatric

Vincristine (TNS-PV).^{76,77} These instruments include both subjective and objective measures of peripheral nerve function, and are completed in five to ten minutes by trained medical personnel (e.g. nurses, physical therapists). Both tools include assessment of reflexes, distal muscle strength, distal light touch (large fiber function), pin sensibility (small fiber function), and pain. Decreased or absent deep tendon reflexes are common in children exposed to neurotoxic agents; distal muscular weakness and sensory loss indicate more severe impairment. Currently, no validated measures are available for children younger than five years of age. Nevertheless, clinicians caring for young children should assess reflexes, distal strength, and sensation as able using developmentally appropriate techniques. Similar to young children, there are no validated measures available for children with brain and CNS tumors, highlighting one of many challenges in evaluating neuropathy in these patients. Children with CNS tumors may have pre-existing neurologic deficits or altered sensorium secondary to tumor site, surgery, or radiation. Concomitant cognitive deficits may further complicate patient reports of pain, or changes in sensation or function. Nevertheless, these patients require assessment of neuropathy and impairment, as many are treated with neurotoxic agents, including platinum and vinca alkaloids. In general, quantitative sensory testing and electrodiagnostic testing are reported in the literature,^{5,22,28–32,82,83} but likely do not add additional information necessary for routine clinical care, unless alternate diagnoses are being considered or for research purposes. Interestingly, electrodiagnostic testing generally reveals more extensive motor axonopathy from vincristine therapy in children than in adults.^{5,32}

Functional testing, preferably by trained rehabilitation professionals, should be completed when significant neuropathy or functional impairment are present. In addition to refined measures of strength and sensation, these assessments include joint range of motion measurement, formal gait analysis, estimates of functional capacity (e.g. 6 minute walk test), balance testing, and standardized evaluation of manual dexterity. One widely used and standardized assessment with available age and specific normative values available for comparison is the Bruininks-Oseretsky Test of Motor Proficiency.⁸⁴ These standardized assessments allow for the monitoring and response to management strategies, including rehabilitation, as well as dose reduction or cessation of neurotoxic agents.

Management of neuropathy

Management of neuropathy in cancer populations is challenging. Previous trials have investigated multiple pharmaceutical agents, including supplements such as acetylcarnitine, calcium, glutamine, omega-3 and medications such as amitriptyline, amifostine, oxycarbazine, and venlafaxine for prevention and/or remediation of chemotherapy-induced peripheral neuropathy.⁸⁵ However, studies have largely been conducted in adults and either demonstrate no benefit or are inconclusive due to insufficient sample size or difficulty in specific attribution to multi-agent treatment using neuropathic agents. The American Society of Clinical Oncology Clinical Practice Guideline (2014) concludes that no agents have demonstrated sufficient evidence to support use for the prevention of chemotherapy-induced peripheral neuropathy in adults with cancer.⁸⁵ For those who develop neuropathy, data support (moderate recommendation) the use of duloxetine for paclitaxel- or oxaliplatin-induced pain.⁸⁶ However, this agent has not been evaluated in pediatric patients

or in persons with vincristine-induced neuropathy. Current and past randomized trials in pediatrics investigating any pharmaceutical interventions for pediatric patients are few, and are mostly limited to patients with vincristine-induced neuropathy (Table 4). Tricyclic antidepressants (e.g., nortriptyline), gabapentin, and a compounded topical gel containing baclofen, amitriptyline, and ketamine have been suggested based on their utility in other populations with neuropathic pain.⁸⁵ Gabapentin is associated with pain reduction in patients with moderate or severe neuropathic pain from post-herpetic neuralgia or painful diabetic neuropathy.⁸⁷ Both gabapentin and pregabalin have been used in several pediatric studies of vincristine-induced neuropathy, but their efficacy has not been unequivocally established.^{80,88}

In pediatric settings, dose reduction or treatment interruption is often considered to prevent or treat chemotherapy-induced neuropathy. For example, the maximum single dose of vincristine is typically capped to 2.0 mg, regardless of body surface area, because the incidence of neuropathy increases above this dose.²⁰ If vocal cord paralysis, motor paralysis, severe neuropathic pain, severe abdominal cramps, typhilitis, or syndrome of inappropriate antidiuretic hormone secretion develop, vincristine is often withheld or dose-reduced.^{20,89} However, because vincristine is an important component of curative therapy, vincristine therapy should be resumed and/or dose-escalated as tolerated.⁹⁰ Established guidelines for dose reduction or interruption are lacking, and current practices are widely variable across treatment protocols and clinician preference. The presence of underlying hereditary sensorimotor neuropathy (e.g., Charcot-Marie-Tooth disease) can lead to permanent and/or life-threatening adverse effects after administration of vincristine. These children require alternative therapy.⁹¹ Genotype-based dose adjustment,² shorter treatment duration, and/or longer intervals between treatment may also reduce long-term toxicities. Liposomal vincristine has been marketed as a potentially less neurotoxic formulation, but this has not been established in rigorous clinical trials, and the cost of this agent is significantly greater than conventional vincristine.⁹²

While pharmacological therapy may attenuate pain symptoms, preliminary research also supports the use of non-pharmacologic interventions in children with cancer who develop neuropathy.⁹³ Tanner et al,⁹⁴ in a pilot study, demonstrate preliminary efficacy of using ankle foot orthosis (bracing) to address loss of ankle range of motion, weakness, and associated gait abnormalities among seven children with peripheral neuropathy during cancer therapy, and suggest potential “weaning” of the orthoses after treatment ends. In addition, Casonova-Garcia et al⁹⁵ provides support for use of guided imagery to control neuropathic pain among six children during cancer therapy. Several studies in adult cancer populations also suggest approaches that are likely to translate to pediatric settings. One reported a positive impact of exercise on neuropathy symptoms among 355 adults (93% female, 79% breast cancer) during neurotoxic chemotherapy exposures,⁹⁶ and another, an improvement in both neuropathy symptoms and postural control as a result of balance training in 25 adults with cancer who had evidence of neuropathy.⁹⁷ More work is needed in the study of these non-pharmacologic interventions in the pediatric population.

Rehabilitation strategies for children with chemotherapy-induced peripheral neuropathy should focus on remediation of impairments (postural control deficits,^{98,99} gait

abnormalities, muscle weakness, loss of fine motor skills), support the continued development of motor control (jumping, running, stair climbing), and promote regular physical activity. In addition, loss of sensory function needs to be addressed with patient/family education. In children who develop hypersensitivity to light touch, desensitization treatments may also be helpful.

Conclusion

Peripheral neuropathy is a prevalent toxicity of chemotherapy, including vinca alkaloids and platinum agents, in children with cancer. Depending on the type of nerve tissue damaged, symptoms may manifest as motor, sensory, and/or autonomic. The recommendation to screen all patients receiving neurotoxic agents allows for the prompt initiation of management strategies. Importantly, even after cessation of therapy and optimal management, neuropathy may persist. Future research is needed to further understand how inherited genetic variants contribute to the susceptibility to and severity of peripheral neuropathy secondary to cancer therapy. Furthermore, improvements in surveillance strategies, in particular for young children and those with CNS tumors are needed. Also, further research in pharmacologic agents for prevention or treatment, and rehabilitation interventions are needed which allow for the simultaneous delivery of optimal cancer therapy and the mitigation of toxicity resulting in pain and functional impairment.

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Key Messages

- Peripheral neuropathy is an adverse effect of chemotherapy that can result in dose limitations and choice of therapy, and persist into survivorship
- Manifestations of neuropathy can be motor, sensory or autonomic, and include loss of reflexes, pain, weakness and gastrointestinal symptoms
- Screening for neuropathy should be done on an ongoing basis in all pediatric patients receiving neurotoxic therapy
- Further research is necessary to develop better strategies for treatment and remediation of peripheral neuropathy

Figure 1. Sites and mechanisms of action of neurotoxic chemotherapeutic agents

Chemotherapeutic agents can contribute to peripheral neuropathy across multiple sites of the peripheral nervous system. Agents that exert effects on the dorsal root ganglion (DRG) preferentially cause sensory neuropathies.

Figure 2. Screening and evaluation of pediatric chemotherapy induced neuropathy
Dotted arrow indicates optional assessment pending exam and clinician suspicion.

Table 1.

Characteristics of peripheral neuropathy by type

Type of neuropathy	Distribution	Symptoms	Common manifestations
Motor	Symmetrical or asymmetrical	Muscle weakness, atrophy, cramping, muscle twitching, and decreased reflexes	Gross motor development lost or delayed
Sensory	Symmetrical, distal, “glove and stocking”	Paresthesias, numbness, temperature intolerance, and exaggerated discomfort	Jaw pain, balance problems
Autonomic		Orthostatic hypotension, gastrointestinal disturbance	Constipation or diarrhea

Table 2.

Class of chemotherapeutic agents commonly used in pediatrics, diagnoses they are used for, and primary neuropathy seen

Class of agent	Drugs	Common diagnoses	Primary neuropathy
Vinca domain microtubule-targeting drugs	Vinca-alkyloid • Vincristine • Vinblastine • Vindesine • Vinorelbine	<ul style="list-style-type: none"> • Acute lymphoblastic leukemia • lymphoma • neuroblastoma • Wilms tumor • rhabdomyosarcoma • Ewing sarcoma • medulloblastoma • low-grade glioma • desmoid tumors • retinoblastoma • non-small cell lung cancer 	Motor and/or sensory
Microtubule stabilizing agents	Paclitaxel Docetaxel	<ul style="list-style-type: none"> • ovarian cancer • breast cancer • head and neck cancer • lung cancer • Kaposi sarcoma • cervical cancer • pancreatic cancer 	Sensory
Non-microtubule active drugs	Bortezomib Platinum agents • Cisplatin • Carboplatin • Oxaliplatin	<ul style="list-style-type: none"> • germ cell tumors • osteosarcoma • neuroblastoma • medulloblastoma • low-grade glioma • retinoblastoma • myeloma • non-Hodgkin lymphoma 	Sensory

Table 3.

Characteristics of electrophysiological findings among pediatric cancer populations during, and off treatment

Article	Patient Population	Timing of Testing	Neurotoxic Agent	CV – Motor Nerves Assessed: % abnormal	CV – Sensory Nerves Assessed: % abnormal	CMAP Nerves Assessed: % abnormal	SNAP Nerves Assessed: % abnormal
On-Treatment							
Kavcic et al 2017 ²⁹	Mixed Tumor Types (67% ALL) n=39 Age: 10 ± 6.4	After minimum of 4 doses	Vincristine	Median, ulnar: 7% Tibial, peroneal: 11%	Median, ulnar: 48% Sural: 7%	Median, ulnar: 33% Tibial, peroneal: 48%	Median, ulnar: 67% Sural: 11%
Yildiz & Temucin 2016 ²⁸	Mixed Tumor Types with suspected neuropathy (80% ALL) n=25 Age: mean 7.2 ± 4.8	49.3 ± 28.6 days	Vincristine	Median, ulnar, tibial, peroneal and sural: WNL	Median, ulnar, peroneal and sural: WNL	Median, ulnar, tibial, peroneal and sural: Group data significantly decreased	Median, ulnar, tibial, peroneal and sural: WNL
Toopchizadeh et al 2009 ³⁰	Mixed Tumor Types (60% ALL) n=42 Age: mean 6.2	5 weeks after initiation of chemotherapy	Vincristine	Median, Tibial: WNL	Median, Sural: WNL	Tibial, median, and ulnar: ALL 96% Other cancers 52.9%	Median, ulnar, Sural: WNL
Off Treatment							
Kandula et al 2018 ³¹	Mixed tumor types (52% Leukemia) n= 121 Age: median 16 (range 7–47)	Median 8.5 years (1.5 – 29)	Vincristine or Platinum	-	Sural: WNL	Tibial and Peroneal: WNL	Median: WNL Sural: Vinc 18% Plat 39%
Tay et al 2017 ²²	ALL n=101 Age: mean 11.8 ± 3.8	>2 years	Vincristine	Common peroneal, tibial, median, ulnar: 61.4% *	Sural, median, ulnar, radial: 55% *	Common peroneal, tibial, median, ulnar: 61.4% *	Sural, median, ulnar, radial: 55% *
Jain et al 2014 ³²	ALL n=77 Age: mean 11.2 ± 3.9	within 3 years	Vincristine	Peroneal, Tibial, Median, and Ulnar: WNL	Sural, Ulnar, Median: WNL	Median, Ulnar: 7.8% Peroneal, Tibial: 50.7%	Sural, Ulnar, Median: WNL
Ramchandren et al 2009 ⁵	ALL n=37 Age: mean 14.4 ± 2.8	>2 years	Vincristine	-	-	Median: 8% Peroneal: 21%	Median: 5% Sural: WNL

* Unclear if abnormality reported was CV or amplitude, ALL Acute Lymphoblastic Leukemia, CMAP Compound Muscle Action Potential, CV Conduction Velocity, SNAP Sensory nerve action potential, WNL Result was Within Normal Limits

Table 4.

Characteristics and measured outcomes of randomized controlled trials for peripheral neuropathy or neuropathic pain in pediatric oncology patients

NCT Number	Intervention	Diagnoses	Chemotherapy	Ages	Measured Outcomes
NCT01506453	Gabapentin	Acute lymphoblastic leukemia	Vincristine	1-18 years	- daily total dose of oral morphine (mg/kg/day) - current pain score - pain score in previous 24 hours -
NCT00369564	Glutamic acid	Wilms tumor Rhabdomyosarcoma ALL Non-Hodgkin lymphoma	Vincristine	3-20 years	- Neurotoxicity - Frequency and type of neurotoxicity - Ability to receive all scheduled doses of vincristine
NCT00365768	Glutamine	Leukemia Solid tumors Medulloblastoma	Vincristine	5-21 years	- Incidence of vincristine-induced peripheral neuropathy - Number of participants with progression of neuropathy
NCT00112996	Alpha-Lipoic Acid	Solid tumors	Cisplatin Oxaliplatin	Any	- Severity of neuropathy - Group differences in change scores - Number of courses received - Optimal tumor response