EVALUATION OF PERIPHERAL NEUROPATHY AMONG CHILDHOOD CANCER PATIENTS

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ABSTRACT

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The principal toxicity for children who receive vincristine for the treatment of acute lymphocytic leukemia (ALL) is peripheral neuropathy, with symptoms that negatively affect physical function and may require the reduction or withdrawal of chemotherapy; even though cumulative dosing has not been shown to increase peripheral neuropathy. This population not only has to deal with the physical challenges of cancer but also can have psychosocial and cognitive effects from treatment. Utilizing secondary analysis, the purpose of this dissertation is to examine peripheral neuropathy (PN) trajectory during the second year of ALL treatment which has not been investigated in children receiving vincristine. Describing these symptom patterns in children carries the potential to guide future targeted nursing interventions. The Symptom Management Model will conceptually guide this three-manuscript dissertation to describe the patients' experience and the development of PN over year two of treatment.

Chapter 2 (manuscript 1) examined the state of the science relative to valid and reliable assessment tools for measuring VIPN in pediatric patients receiving chemotherapy through a review of the literature. The results of the scoping review identified two valid and reliable measures (i.e., Ped-mTNS, mTNS©-PV), with one tool better suited for children (mTNS©-PV).

Chapter 3 (manuscript 2) and Chapter 4 (manuscript 3) involve a secondary analysis using data collected from an observational, longitudinal, prospective, multi-center study, entitled The Advance Trial*,* funded by the National Cancer Institute. Chapter 3 (manuscript 2) characterizes the changes in VIPN in a retrospective sample of 77 children with ALL using the

cumulative score of the modified TNS©-PV (1–20; higher = more severe) monthly at 12, 15, 18, 21, and 24 months and identifies which nerve pathway contributes to a higher VIPN cumulative score using the subscales of the modified TNS©-PV at the aforementioned time points. These results provide evidence that VIPN is persistent during the second year of ALL treatment and that the sensory/motor pathway is affected the most.

Utilizing the same aforementioned data set, Chapter 4 (manuscript 3) examines whether the patient characteristics and treatment characteristics (i.e., race, sex, age, VIPN at 12 months) are associated with VIPN severity at 24 months based on the modified TNS©-PV cumulative score. The modified TNS©-PV scores were not correlated with age, sex, race or VIPN at 12 months. Female sex and VIPN at 12 months are associated with VIPN at 24 months as an interaction. Early identification of patients at risk for severe VIPN will enable nurses to proactively screen and monitor patients for peripheral neuropathy as well as recommend interventions to improve this population's functional status.

Results from this three-manuscript dissertation add to the growing body of evidence showing a high incidence of PN in children, specifically sensory/motor neuropathy, that does not resolve during the second year of ALL treatment. Proactive assessment and early interventions directed toward children at risk to improve their physical function should be investigated. Studies in larger samples are needed to validate these findings. Patient and provider education is vital to prevent injuries and other complications of PN as well as to improve a patient's quality of life and physical functioning. Future research should focus on examining the psychosocial and cognitive disabilities resulting from PN, examining differences in symptom presentation and functioning between boys and girls with PN, and finding more effective means of treatment.

This dissertation is dedicated to my two children, Zachary and Benjamin, who have offered continuous support and made considerable sacrifices in order for me to see the completion of the doctoral program to fruition.

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KEY TO ABBREVIATIONS

ALL	Acute Lymphocytic Leukemia
CIPN	Chemotherapy-Induced Peripheral Neuropathy
CMAP	Compound Muscle Action Potentials
EORTC	European Organisation of Research and Treatment of Cancer
QLQ	Quality of Life Questionnaire
CIPN20	Chemotherapy-Induced Peripheral Neuropathy 20
FACT/GOG-Ntx	Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group Neurotoxicity Subscale
IDEA	Individuals with Disabilities Education Act
IQ	Intelligence Quotient
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Nerve Conduction Studies
NPD	Negative Peak Duration
Ped-mTNS	Pediatric Modified Total Neuropathy Scale
PNS	Peripheral Nervous System
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-Reported Outcome
PTSD	Post Traumatic Stress Disorder
QOL	Quality of Life
TNS	Total Neuropathy Scale
TNS©-PV	Total Neuropathy Scale – Pediatric Vincristine
VIPN	Vincristine-Induced Peripheral Neuropathy

WBC	White Blood Cells
WHO	World Health Organization

CHAPTER 1: EVALUATION OF PERIPHERAL NEUROPATHY AMONG CHILDHOOD CANCER PATIENTS

Introduction

The diagnosis of cancer in children is a life-changing event for the patient and family. Children diagnosed with cancer today have a greater than 80% chance of survival due to the development of new anti-cancer treatments over the past several decades (American Cancer Society [ACS], 2019). Survival has increased so dramatically that supportive care and survivorship have become a focus of caring for children diagnosed with cancer. In the United States more than 3,000 children are diagnosed with acute lymphocytic leukemia (ALL) each year which is the most prevalent cancer in children and adolescents (ACS, 2019). In order to understand the complexity of ALL, the physiological impact, quality of life, and social determinants that impact care will be discussed.

Physiological Impact

Acute lymphoblastic leukemia (ALL) is a disease associated with bone marrow overproduction of white blood cells called lymphocytes and accounts for 29% of childhood malignancies (ACS, 2019; Siegel et al., 2018). Because of the over-proliferation of immature white blood cells (WBCs) in the bone marrow and subsequent crowding out of mature cells such as platelets, red blood cells, and WBCs, affected children are not able to fight infection adequately and thus often present with fever, bruising, and bone or joint pain. The peak incidence of ALL in children occurs between the ages of 3 and 5 years, although children can develop the disease at any age during childhood or adolescence (Hunger & Mullighan, 2015). The incidence varies significantly based on race and ethnic group: 14.8 cases per million Blacks,

35.6 cases per million Caucasians, and 40.8 cases per million Hispanics (Lim et al., 2014). Boys have a higher frequency (55%) of ALL compared to girls (45%; Lim et al., 2014).

Treatment for ALL

Current ALL treatment consists of a multi-agent chemotherapy regimen (i.e., vincristine, dexamethasone, pegaspargase, methotrexate, cytarabine) divided into treatment phases (i.e., induction, consolidation, interim maintenance, delayed intensification, and maintenance), which typically last two years for girls and three years for boys (National Comprehensive Cancer Network, 2016). Treatment regimens are based on risk categories for ALL (i.e., standard, intermediate, high risk and very high risk) developed by the Children's Oncology Group treatment trials (Koh et al., 2018). The most commonly used protocol for ALL standard risk patients is shown in Table 1.1. In Table 1.2, the various protocols are shown including the eligibility criteria. Regardless of the protocol a child is started on, the vincristine dosing is 1.5 mg/m^2 to a maximum dose of 2 mg/m^2.

Five-year survival rates are nearly 90% in the United States (Tai et al., 2017). This profound improvement in survival rates has shifted the nursing focus to mitigating morbidity and survivorship in this population, with increasing attention to short and long-term outcomes affected by toxicities related to treatments including vincristine-induced peripheral neuropathy (VIPN). Clearly, this risk-based approach has reduced mortality, but it has not had effects on the incidence of VIPN (Kandula et al., 2016; Möricke et al., 2008), thus leaving a symptom management gap for nursing research to address.

The improved survival rate of ALL can be attributed, in part, to the use of *Vincristine* (Oncovin®). This drug, one of the most widely used and critically important anticancer agents in killing cancer cells, is delivered by nurses worldwide in the treatment of several common

pediatric cancers, including ALL, despite a profile of highly variable cumulative dose-dependent neurotoxicity, which often results in chemotherapy dose reductions, thereby conceding full efficacy (Kandula et al., 2016; Van de Velde et al., 2017). Prior to 1950, pediatric ALL was uniformly fatal within three months (Demidowicz, et al. 2019; Simone, 2006). Following approval by the FDA in 1963 (Johnson et al., 1963), vincristine quickly became recognized as one of the most effective treatments for curing acute lymphocytic leukemia (ALL); lymphomas; sarcomas; neuroblastoma; and kidney, liver, lung, brain, and breast tumors (Mora et al., 2016). In addition, vincristine is one of the very few chemotherapy drugs used in developing countries because it is not associated with myelosuppression (decreased bone marrow activity) and is relatively low cost (Mwafongo et al., 2014). Vincristine has poor penetration across the blood-brain barrier and into the central nervous system (CNS; Mora et al., 2016); thus, its neurotoxic effects are more prominent on the peripheral nervous system (PNS). Vincristine causes signs and symptoms of peripheral neuropathy in 55% to 100% of children who are exposed to this antineoplastic agent (Lavoie Smith et al., 2015; Gilchrist & Tanner, 2013; Gilchrist et al., 2009) and is the principal toxicity seen in patients receiving it. Symptoms of VIPN include numbness, tingling, neuropathic pain, loss of vibration sensibility, and loss of temperature sensibility (Lavoie Smith et al., 2015). Signs of VIPN include decreased strength and loss of deep tendon reflexes (Lavoie Smith et al., 2015).

Vincristine affects a majority of individuals during the first year of ALL treatment and has been responsible for the decline of physical function and quality of life in pediatric cancer patients (Mora et al., 2016; Robison & Hudson, 2014). Children receive vincristine treatment for a minimum of two years during treatment for ALL (two years for girls and three years for boys); however, the patient experience of peripheral neuropathy (PN) during the second year of

treatment has not been investigated (Mora et al., 2016). Multiple factors which are interrelated influence the prevalence and severity of vincristine-induced peripheral neuropathy (VIPN). These factors include the dose of vincristine administered, the time interval between doses, drug interactions, and the method of administration (Van de Velde et. al., 2017).

Based on the literature, VIPN in adults is considerably more studied compared to pediatric VIPN even though VIPN in children presents a significant healthcare burden with different clinical phenotypes and chronic course during survivorship. Pediatric VIPN is expected to increase in prevalence resulting from improved cancer outcomes in children (ACS, 2019). A systematic review of 61 studies reported significant variability in incidence (20% to 100%) and trajectory of peripheral neuropathy which is the result of assessment and diagnosis of VIPN (Kandula et al., 2016). There may be shared aspects of VIPN in adults and children however there are also distinct aspects that require dedicated studies in children.

"The neurobiology of the peripheral nervous system in children most likely alters how neurotoxic chemotherapies damage axons, the dorsal root ganglia neurons and glial components, including Schwann and satellite cells" (Cavaletti, et al., 2019, p. S7). During childhood, the dorsal root ganglia neurons, axonal diameter, myelination, and axonal density all change thus reaching full maturation (Cavaletti, et al., 2019). Depending on when the child is exposed to the neurotoxic agent, the genesis and course of the VIPN could be affected. For example, children experience predominantly more severe motor neuropathy during year one of treatment for ALL but this has not been seen in adults with VIPN (Kandula et al., 2016; Seretny et al., 2014). The precise mechanism for this difference in adults versus children is unclear however it is suspected that this is due to pharmacokinetics, different neuronal biology, and possibly a lack of early detection of VIPN (Cavaletti et al., 2019).

Afferent and Efferent Neurons

In order to understand the neurotoxic effects on the peripheral nervous system, it is necessary to examine the difference between afferent and efferent neurons. The afferent neurons begin in the periphery such as in the skin and have cell bodies in the dorsal root ganglia. A single axon leaves the cell body and immediately divides into two axon branches. The long branch is directed toward the sensory organ (e.g., skin) and the short branch enters the spinal cord (see Figure 1.1). The long branch ends with peripheral sensory receptors for different types of environmental stimuli. An example of this would be mechanoreceptors can sense touch, pressure, and vibration, thermoreceptors sense heat and cold, and nociceptors sense pain. When an external stimulus such as touch stimulates these receptors, a process of transduction occurs and an electrical impulse is generated in the axon. There are some differences between neurons that carry pain and temperature sensations versus neurons that carry vibration, proprioception and light touch sensations. First are the difference in the peripheral axons. Different types of sensation are carried by various classes of peripheral axons categorized by fiber diameter and myelination, and thus speed of conduction. The largest, heavily myelinated axons (i.e., A-alpha and A-beta) carry sensations of vibration, light touch and proprioception. Smaller, lightly myelinated axons (i.e., A-delta) and very small unmyelinated axons (i.e., type C) carry sensations of heat, cold, and pain. Different sizes of axons may be differentially affected by mechanisms that disrupt axonal function, and thus there may be impairment of small axon function without, or with less, impairment of function of larger axons. After the axons enter the spinal cord through the dorsal roots, there is one pathway for neurons carrying vibration, proprioception and light touch sensations, and a different pathway for pain and temperature neurons to reach the thalamus and cerebral cortex to mediate various sensory perceptions.

The peripheral nervous system efferent neurons are the axons of the spinal cord motor neurons that carry motor impulses from the spinal cord ventral horn to the skeletal muscle effector organs thus facilitating muscle contraction. The cell body of the efferent neurons, located in the ventral horn, gives rise to one long axon which develops neuromuscular junctions with the muscle (see Figure 1.1). The motor neurons in the ventral horn receive input from motor neurons that have cell bodies in the brain cerebral cortex.

To produce deep tendon reflexes, afferent sensory neurons from muscle spindles stimulated by tapping the tendon enter the spinal cord through the dorsal root, and directly synapse with motor neurons in the ventral horn (shown in Figure 1.1). Efferent motor neurons travel to the appropriate muscle fibers to cause contraction to produce the reflex. A decrease in deep tendon reflexes can be caused either by deficits in the sensory component, deficits in the motor component, or both.

The biological mechanisms contributing to the development of VIPN remains unclear; however, studies in murine models demonstrate axonopathy and microtubule dysfunction in its progression (Geisler et al., 2016). Microtubules are small tubes composed of thirteen filamentous strands (Starobova & Vetter, 2017). Each filament is made up of a chain of two proteins, alpha and beta tubulin (Staff et al., 2017; Starobova & Vetter, 2017). Vincristine binds to the beta subunit of tubulin and inhibits microtubule formation. Microtubule aggregation from bound vincristine leads to axonal swelling, which impairs axonal transport and causes dying back of the nerve from distal to proximal aspects (Carozzi et al., 2015; Landowski et al., 2016; Prior et al., 2017).

Based on the negative physiological impact associated with VIPN, there is strong evidence that nursing research is needed to understand how to effectively decrease the morbidity

burden in these children (Essig et al., 2014; Fardell, et al., 2017; Robison & Hudson, 2014). In addition, effective nursing interventions need to be developed to optimize health and well-being for children affected by this troublesome condition. Next, the impact on a child's quality of life will be discussed.

Quality of Life

Health-related quality of life (HRQL) is a multidimensional concept that includes physical, psychological, and cognitive domains and characterizes how individuals and families perceive the impact of the disease on the child's health and well-being (Fardell et al., 2017). It is important to measure treatment-related toxicities and their impact on the patient and family. A recent systematic review of HRQL in children undergoing treatment for ALL included 22 studies in which all reported lower HRQL outcomes compared to healthy controls (Fardell et al., 2017). Two studies found that HRQL in children with ALL improved over the treatment phases toward treatment completion; however, these children continued to have lower HRQL compared to healthy controls (Furlong et al., 2012; Mitchell et al., 2016). Nine studies found that HRQL improved longitudinally over time during survivorship (Fardell et al., 2017). Since HRQL has been measured in adults experiencing chemotherapy-induced peripheral neuropathy (CIPN), it would be important to compare these findings to children experiencing CIPN. HRQL has not been measured in children yet experiencing peripheral neuropathy due to cancer treatment.

Physical Impact

Multiple studies provide strong evidence to support that pediatric cancer survivors experiencing VIPN have impaired physical functioning during treatment and post-treatment for ALL (Gilchrist & Tanner, 2016; Gilchrist et al., 2017; Kandula et al., 2018; Ramchandren et al., 2009; Tay et al., 2017). A single center study with 47 children undergoing active treatment

demonstrated significant reductions in muscle strength ($P < 0.001$), grip strength ($P < 0.001$), muscular endurance of legs ($P = 0.035$), hand-eye coordination ($P < 0.001$), static balance ($P < 0.003$), speed ($P< 0.012$), and flexibility ($P < 0.001$) based on the MOON test used for measuring motor performance in pediatric oncology patients (Götte et al., 2015). In a more recent cross-sectional observational study of 121 childhood cancer survivors, 66% of children demonstrated impaired manual dexterity and 33% exhibited impaired balance (Kandula et al., 2018). Children had difficulty with light touch sensation and manual dexterity. In yet another study (Ness et al., 2012), the most common physical limitation reported was difficulty walking which was found in 46.5% of children (Ness et al., 2012). Only 15.4% of the participants demonstrated poor balance, but overall 54.5% of the children had one or more physical limitations (Ness et al., 2012). Children were found to have a slower velocity, decreased step length, and a decreased cadence based on data collected via a GAITRITE walkway (Gilchrist & Tanner, 2016). Only a few studies measured upper extremity function; thus, under-reporting may be occurring in the pediatric population regarding sensory or motor functional impairments (Kandula et al., 2018; Ness et al., 2012).

Adult patients self-report a variety of painful and non-painful chemotherapy-induced peripheral neuropathy (CIPN) symptoms that affect their ability to perform activities of daily living. More than half of patients report numbness, tingling, neuropathic pain, loss of balance and generalized weakness (Tofthagen, 2010). As a result of a decline in lower extremity strength and loss of sensation, 43% of adult patients required the use of an assistive device for walking as the result of CIPN (Tofthagen, 2010). Many adult patients develop such severe impairment that they are no longer able to work or exercise and report disruption in their hobbies, leisure activities, and familiar roles (Bakitas, 2007; Tofthagen, 2010).

An impairment in physical function leads to increased risk of falls and other forms of accidental injury. In adults, patients with chronic CIPN have increased injury resulting from sensorimotor impairment involving weakness, diminished sensation, altered gait, and poor balance (Tofthagen et al., 2012). Similarly, children may injure themselves and not even realize they have been injured until visual inspection shows a bruise or cut (Tofthagen, 2010). The evidence in adult patients with chronic CIPN who experience increased rates of falls and accidental injury due to their impairments provides support that children most likely will also have increased risk of falls and accidental injury. Children who develop VIPN with loss of physical function will have increased need for assistance with basic activities of daily living (e.g., self-care or mobility) and may need assistive devices to remain active (Javalkar et al., 2017).

Psychological Impact

Nearly 60% of children diagnosed with ALL and their parents suffer significant psychological morbidity compared to healthy controls (Khalifa et al., 2014). Childhood and adolescence typically are a time of growth, opportunity, and accomplishing important developmental milestones. Children receiving ALL treatment can experience disruption in their emotional development that may adversely affect their future (Vetsch et al., 2018). Although this dissertation is focused on physical signs and symptoms, it is important to understand the psychological consequences of cancer treatment in children. This section will highlight the impact of cancer and its treatment on the emotional and psychological growth of a child during each developmental stage and highlight common issues across the treatment continuum.

Erikson (1964) conceptualizes five growth stages (i.e., trust vs. mistrust, autonomy vs. shame/doubt, initiative vs. guilt, industry vs. inferiority, identity vs. role confusion) that a person

accomplishes in childhood and adolescence. A childhood diagnosis of ALL can interrupt attainment of one or more of the psychosocial developmental milestones given the high psychological demands that such a threatening illness and its subsequent treatment place on normative life experiences (Meeske et al., 2001).

A child between the ages of 3 and 5 years, based on Erikson's (1964) Stages of Psychosocial Development, would be in the preschool stage of initiative versus guilt (Brand et al., 2017). The goal of this stage is for the child to initiate activities, develop independence, and develop control over their world through social interactions which can be very difficult in the context of medical treatment. Children learn to make and achieve personal goals that help them develop self-confidence and a sense of purpose in life. When a child is diagnosed with ALL, they are removed from preschool or school in order to begin cancer treatment. The initiation of treatment requires a significant amount of adaptation on the part of the child and family including changes in the daily routine, unexpected events, financial costs, and worry about the possibility of death (Brand et al., 2017). The child is often isolated from their peers and social network, and their daily routine is changed dramatically. If a child is unsuccessful at achieving the developmental markers associated with this stage, they can develop feelings of guilt, have low self-confidence, or lack a sense of purpose in life (Meeske et al., 2001). This could potentially alter or impede psychosocial development growth for the cancer survivor.

The next stage of industry vs. inferiority that coincides with the early school years (ages 6-12 years) describes the development of a sense of competence as a critical task (Erikson, 1964). School plays a central role and helps to facilitate the development of emotional, cognitive, and social growth (Brand et al., 2017). Children develop social hierarchies during this stage and begin to measure themselves against their peers. They desire friendships and want to belong to a

group (Brand et al., 2017). A lack of academic success during this stage may cause a child to feel inadequate (Erikson, 1950). If the child cannot believe in his or her own abilities, their ego suffers, and they may abandon hope of being a productive adult. The child may feel insignificant or powerless. The distortion of perceived progress in this stage can result in impaired emotional autonomy, future economic autonomy, and educational and vocational planning, all of which have been described in pediatric cancer survivors (Hinds et al., 2007; McGrath & Rawson-Huff, 2010; Pound et al., 2012). Returning to school as soon as possible can promote positive adjustment.

Adolescents have unique challenges that occur as the result of their developmental stage. The hallmark of adolescence is the ability to develop an identity (Brand et al., 2017). Many teens self-report that they just want to be "normal" (D'Agostino et al., 2011). According to Erikson (1964), their developmental stage coincides with identity vs. role confusion; characterized by challenges related to self-image, developing a capacity for intimacy, economic and emotional autonomy, and career planning. Patients being treated for ALL can experience delays in identity development and the formation of their self-image (Brinkman et al., 2013). For older adolescents being treated for ALL during the intimacy vs. isolation stage, sexual roles and the capacity for intimacy are also affected.

The psychological difficulties that children face can vary according to their age at the time of ALL diagnosis. Across all age groups, studies have identified delayed social maturation, mood disturbances, post-traumatic stress disorder (PTSD), and relationship problems (Eiser et al., 2000; Fisher et al., 2018). Psychological morbidity resulting from ALL treatment was reported in 86% of a children (N = 43) in the maintenance phase of treatment (year 2 of treatment) for ALL; with individuals affected exhibiting emotional outbursts, physical and verbal

aggression, anxiety, fear, moodiness, and irritability (Kunin-Batson et. al., 2016; Williams et al., 2014). After treatment, cancer survivors are at increased risk for developing depression, anxiety, post-traumatic stress symptoms, and cancer-related worry (Deyell et al., 2013; Kuba et al., 2019). Childhood cancer survivors have a slightly increased risk of being prescribed antidepressants and are more likely to fill antidepressant prescriptions compared to their peers (Deyell et al., 2013; Johannsdottir et al., 2017). In addition, an ALL diagnosis is a traumatic event in a child's life, and there are long-term childhood cancer survivors who meet the criteria for PTSD in survivorship, often decades after their treatment has ended which can lead to diminished quality of life (Brand et al., 2017; Eiser et al., 2000; Fardell et al., 2017; Gurney et al., 2009; Meeske et al., 2001).

Cognitive Impact

In addition to the psychological consequences of cancer, many children also have cognitive difficulties as a result of ALL diagnosis and treatment. The cognitive effects of treatment are directly correlated with the maturation of the brain at the time of treatment, with younger children facing the greatest risk of sequelae (Janzen & Spiegler, 2008; Nathan et al., 2007; Sleurs et al., 2017). In addition to age, the time since treatment is also important. Intellectual functioning and skill attainment decline as time from last treatment increases (Janzen & Spiegler, 2008). Performance and total intelligent quotient are significantly lower in children undergoing treatment for ALL compared to healthy controls. This gap becomes more pronounced in survivors of ALL (Khalifa et al., 2014). This section will highlight the impact of cancer and its treatment on the cognitive development of a child during each stage and discuss common issues across the treatment continuum.

Children ages 2 to 5 years are cognitively in the preoperational cognitive developmental stage according to Piaget's (1962) Cognitive Developmental Theory. In the preoperational stage, children are described as egocentric and magical thinking is the hallmark of this stage. They are not able to abstractly conceptualize. Piaget describes a sub-stage between the ages 4 to 7 that involves intuitive thought. Children in these age groups have transductive reasoning (i.e., belief that two unrelated events are associated) which can impact how children understand their cancer and treatment (Brand et al., 2017).

Children ages 7 to 11 years are in the concrete operations stage, during which they develop the capacity to think logically and understand the viewpoints of others (Brand et al., 2017). This allows them to develop cognitive structures by which to logically explain their physical and emotional experiences. The focus of this stage is cause and effect and fairness (Brand et al., 2017). Children often develop fear during this stage thus it is important to ask the child what their understanding of cancer is so any misconceptions can be resolved (Brand et al., 2017). Children need to know that their actions did not cause the cancer and that a diagnosis of cancer or the development of VIPN is not a punishment for any of their actions (Brand et al., 2017).

Lastly, the adolescent years through adulthood is the formal operations stage when complex reasoning and abstract thought are developed. Moral reasoning and existential thought become apparent at the end of this stage. Adolescents in this stage can understand the risks and benefits of medical treatment, possible complications, and the concept of death (Brand et al., 2017).

Treatment for ALL can negatively impact cognitive abilities over 20 years post-treatment (Kanellopoulos et al., 2016; Weaver & Samkari, 2017). The reason is multifactorial but most

likely includes the high-dose steroids and vincristine that children receive during treatment. Children subsequently exhibit declines in executive function (Kesler et al., 2018), sustained attention (Conklin et al., 2012; Pui et al., 2009), processing speed (Conklin et al., 2012), verbal short-term memory (Moore et al., 2016), and academic capability (Brown et al., 1999; Conklin et al., 2012; Iyer et al., 2015). Additionally, children being treated for cancer have school absenteeism rates more than double those of children with other chronic illnesses, thus impacting their cognitive and interpersonal skills (French et al., 2013). These cognitive late effects, presumed to result from the disease itself as well as treatment, can reduce the patient's quality of life, academic success, and occupational achievement (Gurney et al., 2009; Mody et al., 2008).

The cognitive stage of a child significantly impacts the ability of nurses and researchers to accurately measure VIPN. A young child may not be able to conceptualize what is meant by the terms tingling or numbness when asked. In contrast, older children may be able to describe painful peripheral neuropathy or numbness and tingling in the hands and feet (Lavoie Smith et al., 2017).

Family and the Caregiver

In addition to the impact of cancer and treatment on the child, the family and caregivers are directly affected. A caregiver is any lay person, including family and friends, who provide unpaid assistance to a patient at home with a chronic or disabling condition, such as ALL, and this person is identified by the patient as their caregiver (Wyatt et. al., 2017). The complex medical regimens of children with ALL have a significant negative impact on families and households. Based on the current trends in healthcare, cancer care and the basic activities of daily living are increasingly being provided in the home setting by caregivers (B. Given et al., 2001; C. Given, 2019; Wyatt et. al., 2017; Wyatt et al., 2012). As evidence indicates, women are

the main caregivers providing physical, psychological, spiritual, and emotional care for the child (McCann et al., 2012). High levels of caregiver burden are correlated with negative health consequences and poor quality of life for both the parent and the child (Javalkar et al., 2017). Caregivers of children with cancer may experience increased stress and illness, poor sleep quality, family conflict, strained marital relationships, anxiety, depression, financial stress, poor quality of life, and even premature death (Bajjani-Gebara et al., 2019; Javalkar et al., 2017). However, there is additional evidence reporting positive outcomes for parents of children with cancer who have closer relationships and deeper bonds with their ill child compared to healthy children within the family (Long & Marsland, 2011). Parents tend to be overprotective, indulgent, and provide less discipline to the ill child compared to a healthy child which may lead to behavioral issues for the child with cancer (Bajjani-Gebara et al., 2019; Davies et al., 1991; Hillman, 1997). While the evidence is mixed, there are more studies supporting negative consequences for the informal caregiver putting them at increased risk regarding their well-being.

Social Determinants

Social determinants of health are designed to identify and create physical and social environments that promote good health for all (Lipman & Lobo, 2017). Social determinants can significantly impact care for cancer patients. For this population of ALL children, the following will be considered: healthcare, access to healthcare, economic stability, and legal implications.

Healthcare

The number of childhood cancer survivors in the United States is more than 420,000 and this number is expected to approach 500,000 by 2020 based on improvements in treatment and supportive care (Robison & Hudson, 2014). Currently, one in 530 young adults is a pediatric

cancer survivor (Phillips et al., 2015; Ward et al., 2014). Children diagnosed with cancer have been identified as a group who use a disproportionate amount of healthcare resources (Bona et al., 2014; Bulut et al., 2019; Simon et al., 2010). Pediatric cancer hospitalizations are eight days longer and cost more than 5 times more than other pediatric conditions (Bona et al., 2014). Another more recent study indicated that 75% of children receiving chemotherapy have unplanned hospital visits and more than 85% of these children are readmitted for fever/infection, pain, and nausea and vomiting (Bulut et al., 2019). This vulnerable population of individuals who most likely will experience adverse health-related quality of life outcomes during their lifetime need frequent and extended surveillance due to their high risk for early mortality from subsequent cancer, cardiac events, and pulmonary conditions (Armstrong et al., 2010; Mertens et al., 2008).

Additionally, pediatric cancer survivors are fairly rare in family practices thus most community providers lack the knowledge regarding potential complications that may arise from treatment for pediatric malignancies (Nathan et al., 2013). Many providers have discomfort in caring for these survivors and prefer to care for them in consultation with oncology specialists which increases healthcare costs and further burdens the specialists. Family practice providers need to be trained to care for these patients and develop a level of competency in pediatric cancer survivorship.

Nurse scientists and neurologists with expertise in the area of peripheral neuropathy continue to work together to create new knowledge for healthcare. The Food and Drug Administration held a public workshop titled Clinical Development Programs for Disease-Modifying Agents for Axonal Peripheral Neuropathy, in February 2013, to address challenges in the development of strategies for prevention, disease treatment, and symptomatic treatment of

distal symmetrical polyneuropathy (DSP) which includes CIPN (Gewandter et. al., 2019). The attendees came to the conclusion that the lack of progression in this field resulted from inadequate instruments as outcome measures used in clinical trials (Gewandter et al., 2019). As a result, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) partnered with the Consortium on Clinical Endpoints and Procedures for Peripheral Neuropathy Trials (CONCEPPT) to begin efforts to develop better measures (Gewandter et al., 2019).

The Oncology Nursing Society is supporting healthcare efforts to care for children with cancer. The overarching priorities of their research agenda include symptom science, health disparities, and palliative and psychosocial care in oncology (Von Ah et al., 2019). More specifically, one of the goals is to characterize symptom variability in presentation, describe the trajectory across various patient populations, and examine factors such as age, sex, and race that may influence patient responses to therapy. This agenda closely aligns with this dissertation work.

Access to Healthcare

Given the health risks for pediatric cancer patients and survivors, access to healthcare is vital. The Institute of Medicine's report in 2003 recognized the importance of lifelong-risk-based healthcare for childhood cancer survivors and for the development of guidelines for surveillance (National Cancer Policy Board & Institute of Medicine, 2003). In response to the IOM, consensus-based guidelines were developed in 2004 and published by the Children's Oncology Group Late Effects Committee, Nursing Discipline, and the Patient Advocacy Committee. The guidelines are currently in version 3.0 (Children's Oncology Group, 2008; Tonorezos & Henderson, 2014). These clinical practice guidelines are based on evidence-based associations

between exposure and late effects to identify high-risk groups that need specialized surveillance and monitoring.

National efforts are underway to better characterize the patterns of utilization of healthcare for pediatric oncology patients, identify financial burdens and access to health insurance through policy initiatives including Healthy People 2010 which is focused on children with special health care needs (Bona et al., 2014). The National Cancer Institute (NCI; 2006) Progress Review Group published its report "Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer" which outlined the outcome disparities and unmet needs of pediatric oncology patients. This report identified that adolescent and young adults with cancer have the lowest level of health insurance coverage than any other group of Americans (White, 2002). As a result, the National Institute of Health (NIH) NCI Cancer Moonshot Initiative was developed to expedite cancer research aims thus making more cancer therapies available to more patients (NCI, n.d.). The 21st Century Cures Act was passed by Congress in December 2016 providing $1.8 billion in funding for the Cancer Moonshot Research Initiatives (NCI, n.d.). This initiative is to increase symptom management research to improve outcomes for pediatric and adolescent cancer survivors and develop new therapies. In addition, the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act of 2018 was passed by Congress in June of 2018 to accelerate and optimize development of childhood cancer treatments which may have less treatment-related toxicities (NCI, 2019).

Economic Impact

Families also experience increased financial burdens that include prevalent work disruptions for the parents and increased out-of-pocket expenses (Pelletier & Bona, 2015). Examples of out of pocket expenses include transportation, additional child care and food. One

U. S. study found that the annual loss of income is approximately 40% for the poorest families illustrating that there is disproportionate economic hardship for families with lower income levels (Bona et al., 2014). More than a third of parents (35-45%) with children being treated for cancer need to quit a job in order to provide care for the child at home (Bona et al., 2014).

In recent years, the development of new cancer treatments including immunotherapy and hematopoietic cell transplantation continue to change the landscape of cancer care with more services being offered in ambulatory care and home settings. Nonetheless, cancer is still the most common cause of disease-related death in children and adolescents (Robison & Hudson, 2014). The increasing demands of care and its associated costs place a greater strain on an already burdened healthcare system. In the short term, nurses should be aware of resources to refer as necessary to patients and their caregivers for financial counseling to connect them with charities, advocacy organizations, and pharmaceutical companies to who can provide grants to offset the costs of cancer care. When third party payers are no longer able or willing to pay for pediatric cancer care, foundations such at St. Jude's Children's Hospital will provide free care (Paris & Hawkins, 2015).

Legal Impact

The policies developed by the various aforementioned groups closely align with current legal requirements for children with disabilities. Children with ALL may have ongoing effects of treatment such as emotional disturbances, learning difficulties, developmental delays, and orthopedic impairment. There is strong evidence that patients who develop severe VIPN during or post-treatment have a decline in their physical function. The laws that protect the rights of children and adolescents with disabilities or impairments include: 1) the Americans with Disabilities Act (ADA); 2) the Individuals with Disabilities Education Act (IDEA); and 3) the

Rehabilitation Act of 1973 – Section 504. The ADA (1990) protects children against discrimination in transportation, communication, government and public accommodations and employment. This is useful to children and adolescents attending public schools. The IDEA (1990) requires that public schools provide "free and appropriate education in the least restrictive environment" for students between the ages of 3 and 21 years of age with a "disabling condition."

School personnel are often unaware of specific toxicities that childhood cancer patients experience and consequently do not make the appropriate adjustments for cancer patients or survivors (Nathan et al., 2007). The Rehabilitation Act of 1973, Section 504, requires all educational institutions receiving federal funding to provide accommodations for students with physical or mental impairment that limits at least one major life activity. Guidelines developed by the Children's Oncology Group (2008) Long-term Follow-up Guidelines Task Force recommend that school-age cancer survivors undergo neuropsychological testing so that appropriate educational assistance can be provided.

Summary

The complexity and impact of ALL on children and families is profound and requires a holistic team approach to their care. The physiological component, quality of life component, and social determinants of health have far reaching ramifications to the child's outcome during and after treatment. Recognition of the predictors of VIPN and proactive VIPN assessment and management are important steps for nurses to be able to have a direct impact on this population. The purpose of this research was to review outcome measures that can be optimized for use in children and to ascertain the differences in incidence, risk factors, and the physical signs and symptoms of VIPN longitudinally during the second year of treatment for ALL among children.

This study will guide future hypotheses for nursing interventions that may positively impact this difficult condition. Future research and nursing interventions are needed to mitigate morbidity for children affected by VIPN.

Statement of the Problem

Children treated for ALL during year two are exposed to vincristine with a principal toxicity to the peripheral nervous system. The effects of vincristine can include acute (during treatment) or chronic (3 months post-treatment) changes in sensation and/or motor function (Smolik et al., 2018). Oncology nurses are aware that peripheral neuropathy is an important and potentially dose-limiting condition to proactively monitor during treatment even though measuring the child's neuropathy is complex and challenging (Al-Atiyyat & Banifawaz, 2018; Lavoie Smith et al., 2014). Because no curative or management treatments for VIPN are known, it is a leading chemotherapy dose-limiting factor throughout ALL treatment (Liu et al., 2016). The cumulative dose of vincristine thus far has not been shown to increase VIPN severity however investigating the second year of ALL treatment as the cumulative dose of vincristine increases in regards to VIPN may provide insight in this area. Measurement tools, symptom trajectory of VIPN, and risk factors for VIPN will be discussed.

Measurement Tools for Peripheral Neuropathy

Several tools have been used to measure VIPN. These measures include: 1) clinician-reported grading scales; 2) objective examination of sensory/motor and motor function; and 3) combined tools with subjective and objective components. Currently, there are no patient-reported outcome measures recommended for use with children. The psychometric properties (e.g., expert content validity, face validity, construct validity, convergent validity, structural validity, criterion-related validity, predictive validity, test/re-test reliability, internal consistency

reliability, intra-rater reliability, sensitivity, and responsiveness) of each of the existing measurement tools will be synthesized in Chapter 2.

VIPN is difficult to measure objectively in younger children because they often are unable to report and describe the severity of clinical symptoms such as numbness, tingling, or pain. Nerve conduction studies (NCS) have been used previously; however, these studies are expensive, take extensive time to conduct, and can be painful to the child. In addition, NCS only measure large fiber nerve injury. The most common tool used by clinicians is the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) neuropathy grading scale (versions 2.0, 3.0, 4.0; Park et al., 2019; Trotti et al., 2003). This scale is frequently used by clinicians and researchers to document adverse events including the severity of VIPN, but it has been criticized for not satisfactorily evaluating peripheral neuropathy for research purposes (McFatrich et al., 2020). The NCI-CTCAE has a small range (from 0 to 4 or 5) thus demonstrating floor and ceiling effects (Cavaletti et al., 2010; Gilchrist et al., 2014). In addition, the NCI-CTCAE has been shown to overestimate motor neuropathy in patients possibly as a result of confounding factors such as fatigue, depression, and cachexia resulting from cancer and cancer treatment (Frigeni et al., 2011; McFatrich et al., 2020). Two other instruments commonly used in research are the Pediatric Modified Total Neuropathy Scale (Ped-mTNS; Gilchrist at al., 2014; Gilchrist et al., 2009) and the Total Neuropathy Scale – Pediatric Vincristine (TNS©-PV) (Lavoie Smith et al., 2013; Lavoie Smith et al., 2015). Both of these instruments have combined subjective and objective components to screen and assess for VIPN. The Ped-mTNS is concerning for having possible psychosocial adverse effects resulting from pin prick testing which can be distressing to children. The TNS©-PV is the only tool developed and tested specifically for use in children receiving vincristine (Lavoie Smith et al., 2013; Lavoie Smith et

al., 2015). This is also the only scale that differentiates between upper and lower extremity peripheral neuropathy and has higher scores (more severe VIPN) if the patient has upper extremity neuropathy. The composite score of the TNS©-PV has a much larger range of values (from 0 to 28) compared to the NCI-CTCAE. A modified TNS©-PV will be used for this dissertation. The laryngeal and autonomic items were removed from the 7 item TNS©-PV because of suboptimal item-to-item correlations therefore these symptoms may have a different origin. By eliminating these two items (i.e., autonomic/constipation, laryngeal/ hoarseness) the α coefficient improves from 0.68 to 0.84 making this tool a valid and reliable tool for use in children. The removal of these two items creates a modified Total Neuropathy Score - Pediatric Vincristine (mTNS©-PV) which is optimal for use in children receiving vincristine.

VIPN Trajectory

There is mounting evidence that childhood VIPN differs in presentation, incidence, and prognosis compared to adult VIPN, thus the trajectory of childhood VIPN needs to be investigated (Howard et al., 2014; Lavoie Smith et al., 2015). Using the Pediatric Modified Total Neuropathy Scale (Ped-mTNS) to assess prevalence rates during treatment, VIPN is found in 55-87% of children during the first year (Gilchrist & Tanner, 2013; Gilchrist et al., 2009). Based on the Total Neuropathy Scale – Pediatric Vincristine Scale (TNS©-PV), the prevalence rate of VIPN in the first year is 78% (Lavoie Smith et al., 2015). A recent systematic review reported the VIPN prevalence rate during the first year of treatment as 78% to 100% and neuropathic pain was seen in up to 35% of patients (Kandula et al., 2016). More severe or disabling VIPN occurs in approximately 10% of children described as Grade 3 or 4 on the NCI CTCAE scale (Kandula et al., 2016). Peripheral neuropathy in adults decreases to 60% after 3 months and 30% at 6 months or more of treatment (Seretny et al., 2014). This reduction in peripheral neuropathy for

adults does not happen for children during their first year of treatment and may in fact not decrease during the second year to treatment. This investigation will determine if similar prevalence rates affect patients undergoing a second year of treatment with vincristine given continued dosing and likely long-term sustained treatment effects.

As patterns of VIPN are examined, some common trends can be detected. VIPN in children during the first year involves prominent motor features including loss of strength and foot drop whereas adults experience mostly sensory peripheral neuropathy (Hou et al., 2018; Kandula et al., 2016). The signs and symptoms most frequently reported include numbness, tingling, neuropathic pain, decreased temperature sensibility, decreased vibration sensibility, reduced deep tendon reflexes (DTR), and decreased muscle strength. The reduction or loss of DTR (i.e., sensory/motor pathway) is the most frequent manifestation of VIPN (Lavoie Smith et al., 2015). This is followed by reduced strength (i.e., motor pathway) and diminished vibration sensibility (i.e., sensory pathway) which peaks at six months (Argyriou et al., 2012; Kandula et al., 2016; Lavoie Smith et al., 2015).

Signs and symptoms often develop after the first dose of vincristine and continue to worsen even after vincristine dosing and frequency is decreased, thus demonstrating what is known as a coasting effect in patients (Lavoie Smith et al., 2015). A coasting effect occurs when patients are no longer receiving the neurotoxic medication, yet the peripheral neuropathy worsens weeks to months later. In adults, 30% of patients develop worsening neuropathy even after vincristine is discontinued (Hershman et al., 2014). In children, VIPN severity, based on the Total Neuropathy Score – Pediatric Vincristine (TNS©-PV), is highest at four months after beginning ALL treatment and does not improve significantly between 8 and 12 months despite a reduction in vincristine dose density (Lavoie Smith et al., 2015). VIPN signs and symptoms

during the second year of treatment have not been well described. It is important to characterize the variability in presentation and trajectory during the second year of ALL treatment in order to determine when interventions for VIPN should be tested. At the end of year one treatment, sensory/motor and motor pathways are the most affected. This may change during year two of treatment.

In addition to understanding the trajectory of VIPN during the second year of treatment for ALL, it is important to examine which type of nerve damage the child is developing as treatment continues over year two and three. Neurologically, vincristine causes loss of structure and function of the peripheral motor and sensory nerves in a distal to proximal distribution during the first year of ALL treatment (Hoffman et al., 2013; Lavoie Smith et al., 2015; Legha, 1986). The three nerve pathways affected are sensory, sensory/motor, motor (Hoffman et al., 2013; Lavoie Smith et al., 2015). VIPN progresses distally to proximally; subjective and objective findings appear first in the toes and feet symmetrically progressing to the ankles, calves, fingers, and hands during the first year of ALL treatment. Common characteristics of sensory neuropathy include numbness, tingling, neuropathic pain, decreased temperature sensibility, and decreased vibration sensibility (Gilchrist et al., 2014; Lavoie Smith et al., 2015; Ramchandren et al., 2009). Sensory/motor neuropathy is characterized as decreased deep tendon reflexes. Motor neuropathy is characterized as decreased strength in the arms and legs. It is critical to characterize longitudinally the effects of VIPN during year two of treatment for ALL, as well as accurately assess, monitor, and develop management strategies for this treatment-related toxicity. Characterizing the second year of treatment in children undergoing treatment for ALL will address a gap in the current science and will provide researchers with more accurate time points and which nerve pathway to target in the development and testing of interventions.

Patient Characteristics Associated with VIPN

Studies show that the risk of developing VIPN during the first year of treatment is especially high for older children (Arzanian et al., 2009; Ceppi et al., 2014; Diouf et al., 2015; Frost et al., 2003; Guilhaumou et al., 2011; Lavoie Smith et al., 2015). Caucasian patients also have increased prevalence and severity of VIPN compared to African-American patients based on first year analysis of VIPN even though dosing remained the same (Diouf et al., 2015; Renbarger et al., 2008). Factors associated with severity of VIPN have not been investigated for the second year of treatment in children with ALL. It is critical to better understand the characteristics of patients with fluctuating symptoms in order to predict patients who, at baseline, are at greatest risk for VIPN, allowing nurses to target more intensive symptom screening and future management approaches. By having such predictive analytics, nurses can support the delivery of anticipatory patient and family education and future management techniques to improve VIPN outcomes.

Study Purpose and Aims

The scientific contribution of this research expands what is known about VIPN in three ways: 1) synthesis of the available evidence and identification of gaps related to assessment tools used to measure VIPN among children; 2) evaluation of the prevalence and severity of VIPN during the second year of vincristine treatment using a valid and reliable measurement tool; and 3) evaluation of patient characteristics that predict more severe VIPN at 24 months into treatment.

Aims

The aims of this research are to:

1. Determine the state of the science relative to valid and reliable assessment tools for measuring VIPN in pediatric patients receiving chemotherapy through a review of the literature.
2. Describe how VIPN changes over time as measured by the cumulative score of the modified TNS©-PV (1–20; higher = more severe) monthly at 12, 15, 18, 21, and 24 months based on a retrospective sample of 86 children with ALL and identify which type of nerve pathway (sensory, motor, or sensory/motor) contributes the most to a higher VIPN score at 12, 15, 18, 21, and 24 months according to the modified TNS©-PV subscales.
3. Explore if any of the patient characteristics (i.e., race, sex, and age) or treatment characteristics at 12 months (i.e., VIPN at 12 months) are associated with VIPN at 24 months based on the cumulative score of the modified TNS©-PV.

Conceptual Framework

This section introduces the conceptual model that guided the design of the study. Information is divided into three parts. Part 1 introduces the original theoretical model and Part 2 introduces the adaptations made to the model for this research study. The adapted model will outline the antecedents, covariates, and outcome variables included in the model. Part 3 describes the operational model including the instrument that was used to collect the data for the secondary analysis on variables included in the model.

Model Introduction

Theories are used to analyze existing knowledge, guide patient management strategies, and systematically conduct studies to inform practice (Walker & Avant, 2019). No conceptual model has been consistently used in the VIPN literature for symptom management. A mid-range

theory that is applied to the VIPN population will provide a framework to understand VIPN symptom management and important related variables.

The Symptom Management Model

The University of California at San Francisco (UCSF) Symptom Management Model (SMM) was designed to "develop the sub-discipline of symptom management across health science disciplines and across health care settings by elucidating and testing a Model of Symptom Management" (Dodd et al., 2001, p. 669). The model has been used to evaluate symptom management in patients with cancer (Chen et al., 2019; Linder, 2010; Ridner et al., 2012; Srinoppadon & Soywong, 2019; Swore Fletcher et al., 2008), HIV (Loades & Kagee, 2019; Spirig et al., 2005; Voss, 2005; Voss et al., 2006), brain injury (Bay & Bergman, 2006), and diabetes (Skelly et al., 2008). The SMM model has guided studies in children with ALL experiencing pain, fatigue, and sleep disturbance (Gedaly-Duff et al., 2006; Van Cleve et al., 2004; Van Cleve et al., 2002) but has not been used to evaluate VIPN in this population. However, due to its established use with other childhood cancer symptoms, the SMM model was selected to guide this study.

The UCSF School of Nursing SMM (presented in Figure 1.2) is a deductive, middle range theory used to identify gaps in symptom management, assess for management barriers, develop and implement interventions, and target future areas of research (Dodd et al., 2001). The overarching premise of the SMM is that effective symptom management requires all three dimensions of the model (i.e., symptom experience, management strategies, and outcomes) to be considered. These dimensions are interrelated, dynamic, and layered on the metaparadigm of nursing science (i.e., person, health/illness, environment). The relationships within the model are conceptualized with bidirectional arrows (see Appendix B for copyright permission).

Dimension 1: The Symptom Experience

The symptom experience is the first of three dimensions in the SMM. It includes the interrelated components of perception, evaluation, and response to symptoms. These three components of the symptom experience dimension are closely related as represented by bi-directional arrows within the model, indicating that they can both affect and be affected by each other (Dodd, et al., 2001). Within the SMM, a symptom is defined as a subjective experience that produces change in "biopsychosocial functioning, sensations, or cognition" in the patient (Dodd et al., 2001, p. 669). Symptoms are the primary focus of the model because they often cause distress to the patient and family. A sign is an objective finding that can be detected by another person or the patient that represents an abnormality indicative of disease. Signs can be incorporated into evaluating the symptom experience if needed to assess disease status or determine the effectiveness of a management strategy. Signs and symptoms are both important indicators of a problem that the patient and nurse should address.

Perception. Perception of symptoms refers to the individual detecting an adverse change from their baseline state, indicating that their experience is different than usual (Dodd et al., 2001). Perception relies on the ability to detect sensory changes requiring intact afferent pathways, as well as intact cortical functions to interpret these signals and process these symptoms as abnormal (Freeman, 1991). Prior experiences can impact a patient's perception of current symptoms. In cases of chronic disease, patients can detect and describe subtleties of their symptom experience (Dodd et al., 2001).

Evaluation. Evaluation of symptoms includes characterizing the symptom with regard to intensity, location, temporal nature, frequency, and affective impact (Dodd et al.,

2001). To provide insight into the symptom experience, it is valuable for the patient and the nurse to characterize a symptom based on severity.

Response. Response to symptoms includes physiological, psychological, sociocultural, and behavioral alterations that can impact the symptom experience (Dodd et al., 2001). For example, response to pain could result in increased heart rate and blood pressure (Middleton, 2003). Response to symptoms can also be influenced by an individual's prior experience with a symptom (Dodd et al., 2001). Repeated exposure to a symptom may either heighten acuity or diminish responsiveness if the patient has become habituated to its presence (Dodd et al., 2001).

Dimension 2: Symptom Management Strategies

Symptom management strategies is a dimension of the SMM that indicates the need for intervention provision and identifies the specifics of "what, when, how much, to whom, and why," which will then guide the clinician or researcher in choosing an appropriate intervention. The goal of symptom management is to "avert or delay a negative outcome through biomedical, professional, and self-care strategies" (Dodd et al., 2001, p. 673). Management strategies can be focused on an individual, couple, family, or group.

The domains of nursing in the SMM (i.e., person, environment, health/illness) can influence the symptom management process (Dodd et al., 2001). Previous experiences with a symptom can impact what strategies a patient will use to manage that symptom. Environmental situations including availability of resources can impact whether a person will seek additional care for a symptom or utilize other resources such as family or friends. Health/illness variables (e.g., comorbidities) may influence the patient's ability to manage their symptoms. If the patient also has cognitive impairment, they may not have the capacity to initiate symptom management

strategies. The bi-directional arrows between the constructs of symptom experience, outcomes, and symptom management strategies indicate that they can be affected by each other (Dodd et al., 2001).

Dimension 3: Outcomes

Outcomes are the third construct in the model which includes functional status, symptom status (continuation of symptoms or resolution), emotional status, mortality and morbidity, costs, and quality of life. Outcomes, as depicted by the bi-directional arrows, can influence the other two constructs of symptom experience and symptom management. For example, if a symptom is not resolved or relieved, patients may need to re-evaluate the symptom or may want to attempt different symptom management strategies. If the symptom resolves, then the evaluation and management of the symptom are no longer needed.

Person, Health and Illness, and Environment Dimensions

Domains of nursing in the model such as person, health and illness, and environment can influence the dimensions in the model which are symptom experience, the symptom management strategies, and/or the outcomes (Dodd et al., 2001). The person variables (i.e., demographic, psychological, sociological, physiological) encapsulate the basic nature of an individual. These variables are dynamic and affect how a person will view and respond to a symptom. Based on the symptom and population of focus, some variables can be modified while yet others are non-modifiable. Sex is a common variable measured that is known to affect many disease outcomes including cardiovascular (Spence & Pilote, 2015), stroke, and physiologic response to pain (Pieretti et al., 2016). Variables for peripheral neuropathy in the pediatric population remain to be fully delineated. Factors such as obesity, poor bone health, and psychosocial health may be part of a complex interaction that limits physical function.

The health and illness domain encompass variables associated with health and illness status which include risk factors, injuries, disabilities, or disease progression (Dodd et al., 2001). The variables included in this dimension can have direct and indirect influences on the relationships with symptom experience, management, and outcomes. Disease progression of cancer will affect the symptom experience and determine the management strategies available to a patient with pain.

The environment domain includes several components (i.e., physical, social, cultural) that can influence the selection of management strategies and outcomes. The SMM theorizes that effective management of a symptom or symptom cluster requires that all three environment dimensions be considered; this aspect of SSM is depicted using bi-directional arrows.

Adherence

The concept of adherence in the model depicts the relationship between management strategies and outcomes. It is defined as "whether the intended recipient of the strategy actually receive or uses the strategy prescribed" (Dodd et al., 2001, p. 674). A lack of adherence can disrupt the relationship between symptom management strategies and outcomes. The three domains of nursing are hypothesized to influence adherence. The person may or may not have personality traits such that they follow directions very carefully and abide by nursing recommendations. The environment may be so chaotic in a child's life that adherence is difficult. The parent may not support or focus on the child's symptom thus leading to adherence problems. Lastly, the child's health may become so poor that adhering to management strategies may be too difficult.

The SMM was chosen because it has been tested in multiple populations, including children, and has been applied to a large range of symptoms. The UCSF Symptom Management

Model (Dodd et al., 2001), adapted for the current study, provided direction for evaluating the proposed relationships between vincristine exposure and the development of VIPN in adolescents and children.

VIPN Symptom Management Model (SMM)

The concepts being examined in this study include the symptom experience and outcomes of VIPN. While the original model included psychological, sociological, and developmental components, the adapted model will focus on the physiological outcomes based on the data available. Future work will need to return to the original model and explore these other important variables that are not part of this dissertation. The UCSF School of Nursing SMM provides a foundation to address the aims of this research. The adapted SMM (presented in Figure 1.3) will be referred to as the VIPN Symptom Management Model (VIPN-SMM). VIPN in this model is defined as peripheral nerve damage characterized by numbness, tingling, neuropathic pain, impaired vibration sensibility, impaired temperature sensibility, deep tendon reflexes, and loss of strength.

Symptom Experience

The *symptom experience* is the first of three dimensions in the adapted VIPN SMM. It includes the patient's perception, evaluation, and response to VIPN. For this study, the patient's perception includes the subjective assessment of the sensory pathway of VIPN. The VIPN evaluation refers to the objective assessment of the sensory/motor and motor pathways, referred to as signs. The VIPN response is not directly measured in this study; thus, it is presented in the model in grey. The two components of the symptom experience dimension, perception and evaluation, are closely related as represented by the bi-directional arrow within the model, indicating that they can both affect and be affected by each other. The presence of the symptom

(frequency) and the severity will be evaluated. The three components (i.e., patient's VIPN perception, evaluation, and response) of the symptom experience dimension are closely related, as represented by bi-directional arrows within the model.

Perception

Perception, or the subjective ability to recognize symptoms, was captured through child self-report or parent-proxy report of the child's sensory symptoms. Lived experiences with a symptom impact how the symptom is perceived. Initially a child may not understand or be able to describe numbness, tingling, or pain. However, a patient who has a history of the symptom may be able to discern subtleties thus evaluate it with more detail (Lenz et al., 1997). The child's perception to peripheral neuropathy is through self-report of numbness, tingling, and pain.

Evaluation

Evaluation of VIPN includes characterizing VIPN with regard to intensity, location, temporal nature, frequency, and affective impact (Dodd et al., 2001). The VIPN evaluation refers to the objective assessment by the nurse of the sensory/motor and motor pathways which includes strength testing and deep tendon reflexes. These are referred to as signs.

Response

Responses to symptoms are not directly measured in this proposed research, however, if they were measured, such an assessment would provide additional insight into the patient's experience. Patients generally report more than one symptom during the induction phase of vincristine treatment, and the effect of multiple symptoms on how patients respond is currently unknown for the VIPN population. Responses can also impact evaluation. A response such as loss of strength may cause patients to evaluate seemingly minor symptoms as more severe. The presence of objective signs such as muscle weakness most likely would influence the reporting

of symptoms. Understanding these relationships can help nurses to design better management strategies for their patients that could decrease negative responses and improve the symptom experience.

Symptom Management Strategies

This study is hypothesis generating to help direct future nursing intervention design once the trajectory of VIPN prevalence and severity throughout year two of treatment is understood. Strategies for managing VIPN symptoms need to be developed and tested as next steps; therefore, this part of the model is represented in grey (Kandula et al., 2016). Symptom self-management strategies for peripheral neuropathy have been discussed in the chronic illness literature including diabetes mellitus, asthma, cardiopulmonary obstructive disease, heart failure, and cancer (Hanlon et al., 2017). Self-management for CIPN in adults has also been described in the literature (Chan et al., 2018; Knoerl et al., 2018; Speck et al., 2012); however, this has not been described in the pediatric VIPN literature.

Outcomes

For the adapted VIPN Assessment Model, VIPN incidence and severity will be measured. The solid unidirectional arrow asserts that the symptom status and outcomes will be directly influenced by the VIPN experience. The SMM did not take into consideration the child's communication needs and their lack of autonomy. One study evaluating the pain experience during the first year of treatment in children with ALL used the SMM and had the parents report pain for children ages 4 to 7 years (Van Cleve et al., 2004). In the adapted VIPN-SMM, a parent or caregiver can interpret the patient's VIPN experience if a patient is nonverbal or too young to understand the questions being asked. However, studies have shown that parents and providers underestimate subjective symptoms of the child (Alcantara et al., 2017; Eiser & Varni, 2013;

Lambing et al., 2017; Porter et al., 2015), which could jeopardize both management and outcomes of VIPN. For this dissertation, data was included from children age 5 to 18 in an attempt to minimize parent by proxy data.

Person, Health/Illness, Environment

In the VIPN-SMM (Figure 1.3), *person* is defined as a child diagnosed with ALL undergoing treatment with vincristine. Each child's VIPN experience is directly influenced by personal characteristics as depicted in the model with a solid unidirectional arrow that include developmental, demographic, psychosocial, and physiological characteristics. The patient characteristics that may influence VIPN severity during the first year of treatment include increased childhood age, female sex, Caucasian race, and an inherited genetic variant (Diouf et al., 2015; Gilchrist & Tanner, 2016; Guilhaumou et al., 2011; Renbarger et al., 2008). The variables of age, sex, and race will be tested to evaluate if they can predict more severe VIPN at 24 months.

The domain of *health and illness* encompasses variables of health and illness status which include risk factors, injuries, disabilities, disease progression, and treatment-related factors. The variables of risk factors, health status, and disease and injury will not be evaluated; thus, they are represented in grey.

The *environment* domain includes several components (i.e., physical, social, cultural) that can influence the selection of management strategies and outcomes. These components will not be measured for this study; thus they are represented in grey. In addition, in the adapted VIPN-SMM, the adherence to management strategies is not directly measured; thus, adherence to an intervention is presented in grey within the model, since it is not a focus of this research.

Summary of the VIPN Symptom Management Model

The VIPN Symptom Management Model (Figure 1.3) provides a clear logical approach to the study of VIPN in children with ALL. The strengths of the model include its significance to nursing and testability. The original SMM has been tested in children with ALL experiencing pain, fatigue, and sleep disturbance (Gedaly-Duff et al., 2006; Van Cleve et al., 2004; Van Cleve et al., 2002). By adapting the SMM, the dimensions and constructs of VIPN will be tested in order to possibly establish the model's usefulness with this difficult condition and array of symptoms.

Adapted Operational Model

Due to the nature of this research, which used secondary data, the adapted VIPN SMM did not fit the linear longitudinal approach needed for this dissertation. The Adapted Operational Model (presented in Figure 1.4) was developed to illustrate the trajectory of VIPN over time, during year two of ALL treatment. In addition, the operational model was designed for the three-manuscript dissertation which includes a literature review and two quantitative studies. Each manuscript has specific manuscript research question labeled as RQ. DA denotes the global dissertation aims.

The Adapted Operational Model is presented from left to right in Figure 1.4. All of the elements from the Adapted VIPN Symptom Management Model are represented. The blue box represents Chapter 2/ Manuscript 1 which is a literature review of assessment tools for chemotherapy-induced peripheral neuropathy in children. This review resulted in the finding that the modified TNS©-PV is the most valid and reliable tool for measuring VIPN in children.

The second box from the right represents the nursing science domain of person which includes the child and child characteristics with variables of age, sex, and race which is a

foundational component of Chapter 4/ Manuscript 3. Persons in the Adapted Operational Model will be described by age (i.e., years), sex (i.e., male, female), and race (i.e., White, non-White).

The center box represents the peripheral neuropathy experience which includes the nerve pathways of sensory, sensory/motor, and motor. The subscale of the sensory pathway is represented by numbness, tingling, and neuropathic pain. The sensory/motor subscale is illustrated by deep tendon reflexes. The motor subscale is represented by the muscle strength item. Perception in the Adapted Operational Model is the self-report data collected by interviewing each child. Patients reported their perceived numbness, tingling, neuropathic pain, temperature sensibility and vibration sensibility. If the child was unable to answer for themselves, the parents were asked to rate their perceptions of the child's symptom experience based on their observations of the child's behavior. Evaluation in the Adapted Operational Model is objective data collected by examining each patient. These components were captured by measuring deep tendon reflexes and muscle strength. VIPN signs were evaluated as more severe as they progress from distal to proximal for diminished reflexes and strength. The peripheral neuropathy experience is a foundational component for the dissertation Chapter 3/ Manuscript 2.

The outcomes box includes the peripheral neuropathy prevalence and severity based on the modified TNS©-PV scores which is foundational for Chapters 3 and 4 of the dissertation. The management strategies component was represented in white which will be areas of future research.

Measurement Tool for Dissertation

Dissertation aims 2 and 3 were developed from data collected using the modified Total Neuropathy Score©. This measure is a multidimensional instrument, developed by Chaudhry and colleagues (1994), to assess the presence, characteristics, and location (distally versus

proximally) of peripheral neuropathy symptoms, as well as the presence, severity, and location of several physical signs. The modified version by Lavoie Smith and colleagues (2013) was developed to assess VIPN in children diagnosed with ALL who are receiving vincristine. The measure has five items and three subscales that quantify subjective numbness, tingling, neuropathic pain, vibration and temperature sensibility. Objective measures quantify muscle strength and deep tendon reflexes. Each item is scored on a Likert-type scale of 0 to 4 scale with higher scores indicating worsening neuropathy. The total cumulative score ranges from 0 to 20.

Item-to-item correlations were moderately strong (r = 0.51- 0.87; Lavoie Smith et al., 2013). Vibration and DTRs were the most responsive items which correlated to the composite TNS©-PV scores (effect size 0.65, $P < 0.0001$). This tool showed good internal consistency. Internal consistency reliability was supported with a Cronbach's alpha coefficient of 0.84 (Lavoie Smith et al., 2013). Hoarseness and constipation items were removed from the original tool because these items did not contribute significantly to the cumulative score. Prior to the removal of these two items, the Cronbach's alpha coefficient was 0.68. Inter-rater reliability was acceptable ($K_w = 0.54$ -0.99) for all items except paresthesia ($K_w = 0.15$). The TNS©-PV is responsive to change over time based on mean TNS©-PV scores and the NCI CTC grading scale between baseline and 15 weeks (Lavoie Smith et al., 2013). Convergent construct validity was moderately strong with cumulative dosage (r = 0.53), vincristine area under the curve (r = 0.41), and when the TNS©-PV was compared to NCI CTC (r = 0.48; Lavoie Smith et al., 2013). Feasibility was demonstrated in school-age children as VIPN could be assessed in 95% of children. Only 48% of children age 3 could provide subjective symptom information (Lavoie Smith et al., 2013).

Summary

This research contributes the following knowledge to the science of symptom assessment for VIPN in children being treated for ALL:

1. Results of a review of literature published between 1966 and June 2019 relative to measurement tools used to assess VIPN in children. This synthesis is reported in Chapter 2 (manuscript 1) and establishes the current state of the science and identified gaps;
2. The trajectory of VIPN over the second year of treatment for ALL and the symptoms associated with patterns of the nerve pathways affected by VIPN. These findings will be described in Chapter 3 (manuscript 2).
3. The patient characteristics associated with more severe VIPN at 24 months from the point of beginning treatment. These findings will be described in Chapter 4 (manuscript 3).

This research contributes to the scientific knowledge of a significant condition that presents as an array of symptoms in children being treated for ALL. The findings can be hypothesis generating for the development of interventions for VIPN and has the potential for application to other pediatric cancer populations. Chapter 5 summarizes the findings of these three research outcomes and synthesizes the conclusions as they contribute to future nursing research, practice, and health policy.

APPENDICES

APPENDIX A:

Tables and Figures

Table 1.1

Standard Risk Treatment Regimen Protocol for Acute Lymphocytic Leukemia

Protocol AALL0932			
Phase and Regimen	Drug	Dose	Schedule (Days)
Induction (35 days)	Intrathecal cytarabine	Age adjusted	1
	Vincristine sulfate	1.5 mg/m^2	1, 8, 15, 22
	Dexamethasone	3 mg/m^2/dose BID	1 through 28
	Pegaspargase	2500 international units/m^2	4
	Intrathecal methotrexate	Age adjusted	8, 29
Consolidation (28 days)	Vincristine sulfate	1.5 mg/m^2	1
	Meraptopurine PO		1 through 28
	Intrathecal methotrexate	Age adjusted	1, 8, 15
Interim Maintenance Therapy (56 days)	Vincristine sulfate IV	1.5 mg/m^2	1, 11, 21, 31, 41
	Methotrexate IV	Age adjusted	1, 11, 21, 31, 41
	Intrathecal methotrexate	Age adjusted	31
Delayed Intensification Therapy (56 days)	Dexamethasone PO or IV BID	5 mg/m^2/dose BID	1-7 and 15-21
	Vincristine sulfate IV	1.5 mg/m^2	1, 8, 15
	Doxorubicin hydrochloride IV	25 mg/m^2/dose	1, 8, 15
	Pegaspargase IV	2500 international units/m^2/dose	4
	Cyclophosphamide IV	1000mg/m^2/dose	29
	Thioguanine PO	60 mg/m^2/dose	29-42
	Cytarabine IV	75 mg/m^2/dose	29-39
	Intrathecal methotrexate	Age adjusted	1 and 29
Interim Maintenance II Therapy (56 days)	Vincristine sulfate IV	1.5 mg/m^2	1, 11, 21, 31, 41
	Methotrexate IV	Age adjusted	1, 11, 21, 31, 41
	Intrathecal methotrexate	Age adjusted	1 and 31
Maintenance Therapy (12 week cycles)	Vincristine sulfate IV	1.5 mg/m^2	1
	Dexamethasone PO BID	5 mg/m^2/dose BID	1-5
	Methotrexate PO	Age adjusted	8, 15, 22, 29, 36, 43 50, 57, 64, 71, and 78
	Mercaptopurine PO	75 mg/m^2/dose	1-84
	Intrathecal methotrexate	Age adjusted	1

Table 1.2

Children's Oncology Group Treatment Protocol Eligibility

Protocol	AALL0932	AALL0331	AALL0232	AALL1131
Risk Stratification	Standard risk B-cell ALL	Intermediate risk B-cell ALL	High risk B-cell ALL	Very high risk B-Cell ALL
Age at diagnosis	1 – 9.99	1 – 9.99	1-9 years of age with WBC > 50,000 10-30 age with any WBC	Eligible age 1-9.99 with WBC > 50,000, testicular leukemia, or CNS 3. Eligible age > 10 with any WBC, testicular leukemia, or CNS 3.
Initial WBC	> 50,000/uL	> 50,000/uL	Variable	Variable
Other qualifiers	No central nervous system involvement (i.e., presence of leukemic blasts in CNS fluid that contains at least 5 white blood cells per microliter), no testicular involvement, no Down's syndrome	Central nervous system involvement is classified. No testicular leukemia eligible. No hypodiploidy eligible.		
Vincristine dosing	1.5 mg/m^2 (2 mg maximum	1.5 mg/m^2 (2 mg maximum)	1.5 mg/m^2 (2 mg maximum)	1.5 mg/m^2 (2 mg maximum)

Figure 1.1

Deep Tendon Reflex Pathway of the Peripheral Nervous System

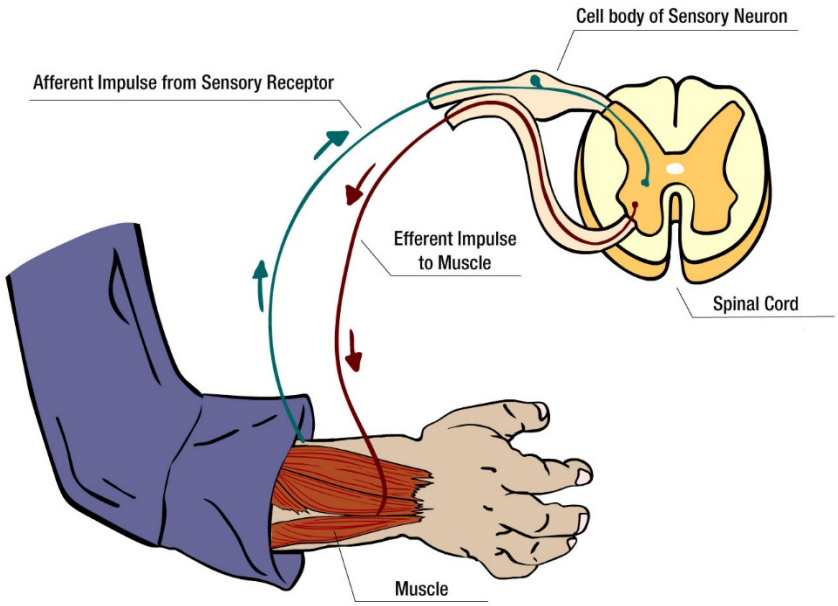


Figure 1.2

The Revised UCSF Symptom Management Model by Dodd et al. (2001)

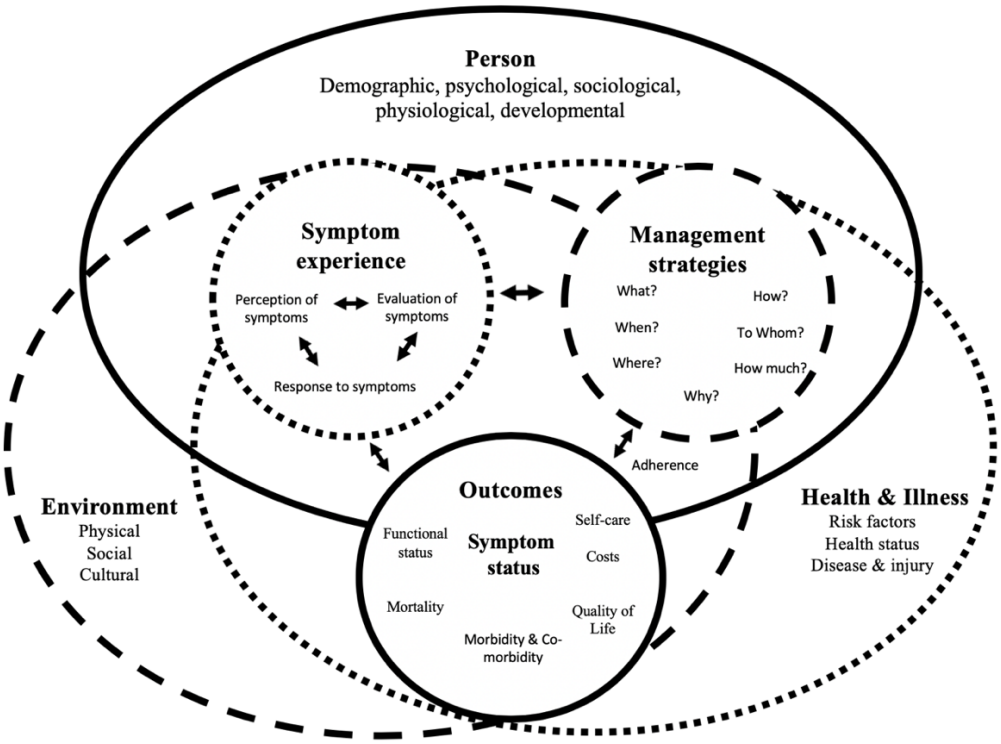


Figure 1.3

VIPN Symptom Management Model

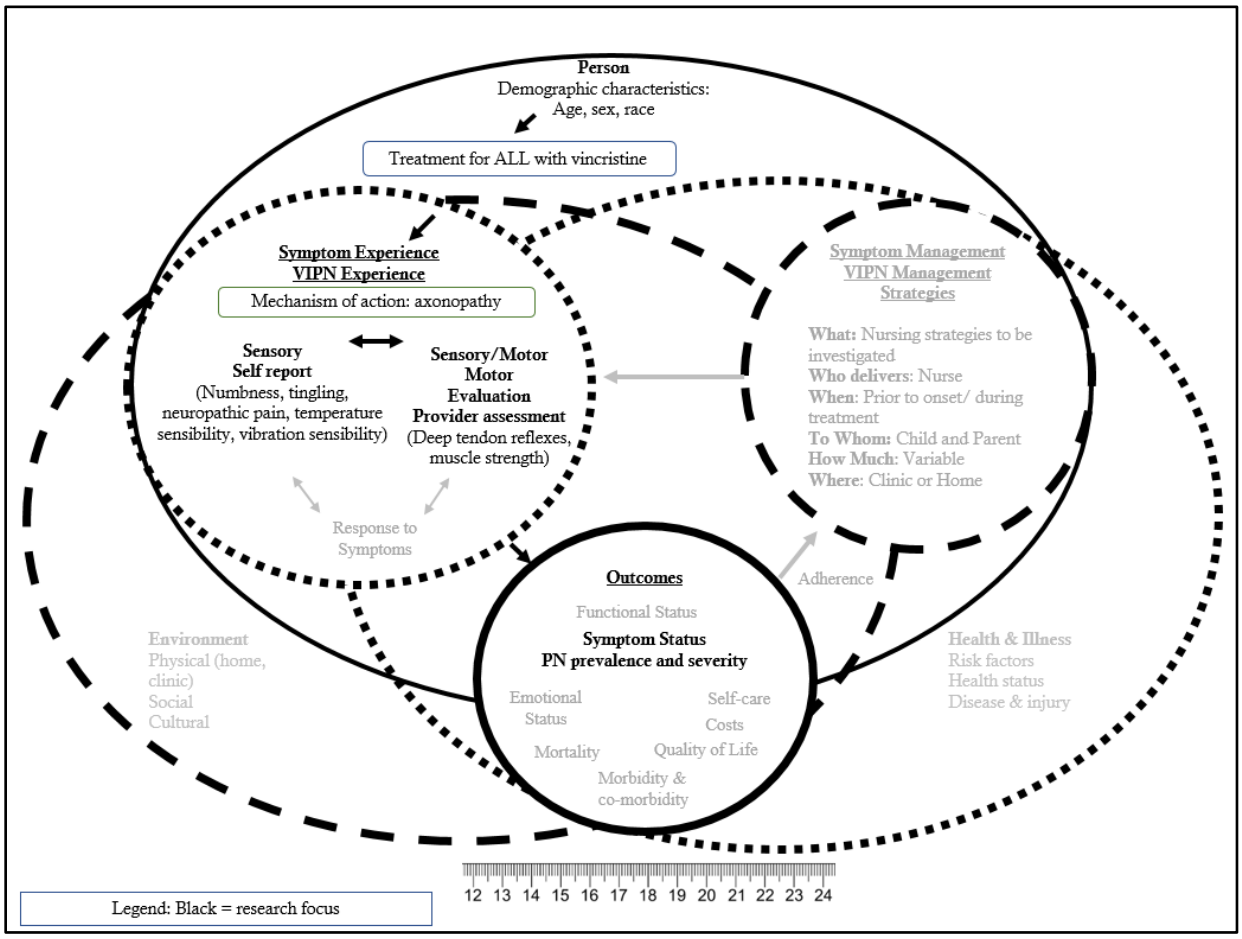
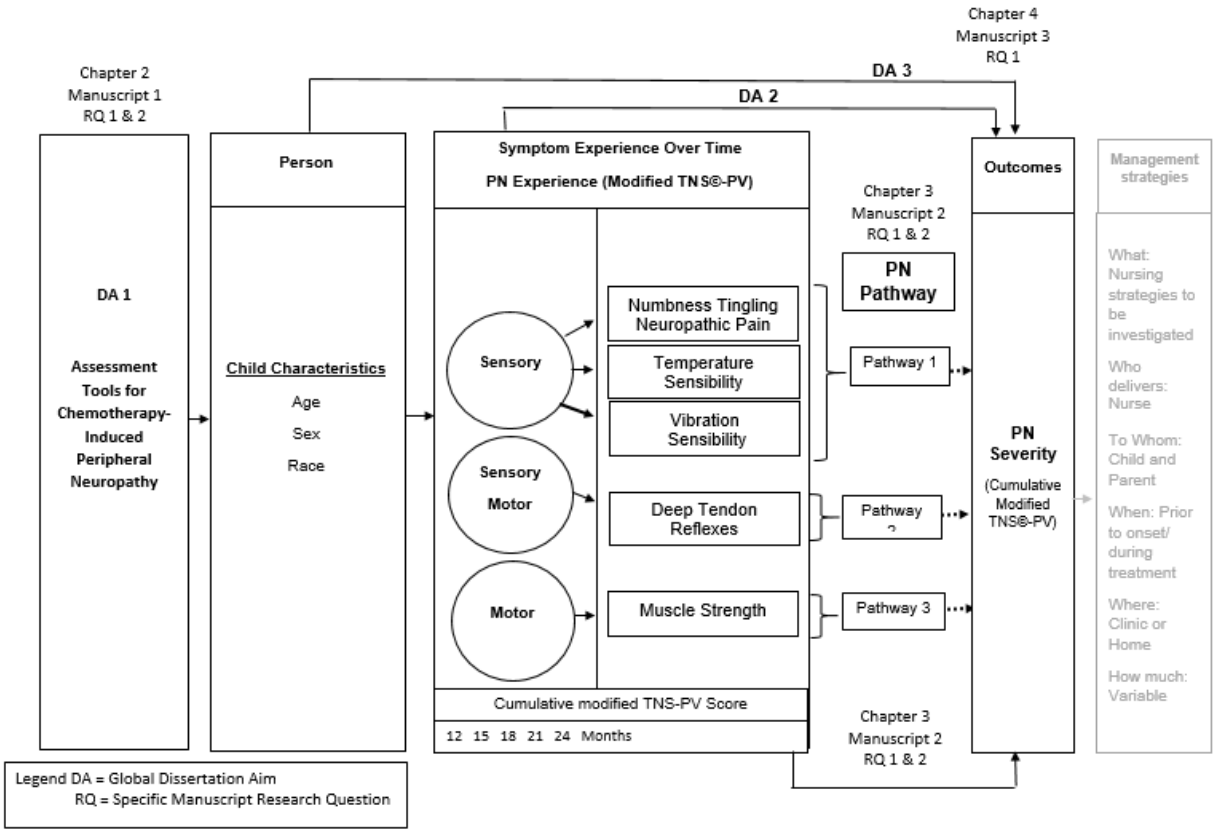


Figure 1.4

The Adapted Operational Model



APPENDIX B:

Symptom Management Model - Copyright Clearance

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CHAPTER 2: INSTRUMENTS EVALUATING CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY IN PEDIATRIC CANCER PATIENTS: A REVIEW OF THE LITERATURE

Abstract

Peripheral neuropathy remains the principal dose-limiting toxicity in children receiving neurotoxic medications (e.g., vinca alkaloids, platinum agents) that often leads to chemotherapy-induced peripheral neuropathy (CIPN). Early identification and measurement of CIPN is a key component to quality care.

This scoping review evaluates pediatric measures and discusses the rationale for selection of measures for CIPN.

Searches of PubMed, CINAHL, EMBASE®, and Cochrane databases were performed for articles published between 1968 and June 2019 that (1) included subjects receiving neurotoxic chemotherapy for cancer and (2) tested psychometric properties of measurement tools used to assess CIPN in children. The quality of each study was assessed using the QUADAS-2 assessment tool to evaluate the risk of bias and applicability of primary diagnostic accuracy studies.

Nine studies met inclusion criteria, with five considered as moderate quality and four considered as high quality. The ped-mTNS is a valid and reliable tool for all phenotypes of childhood CIPN but includes a pinprick test which is not recommended in children. The modified TNS©-PV is the most valid and reliable tool for measuring peripheral neuropathy in children receiving neurotoxic medications based on the psychometric properties of the tool.

To improve the QUADAS-2 scores, additional research is needed with refined inclusion and exclusion criteria, blinding of knowledge of the reference standard while the index test is completed, and improved documentation for the patient selection process.

Two measures (ped-mTNS and mTNS©-PV) have been identified as valid and reliable which can be performed in 10 minutes or less to assess and monitor CIPN during cancer treatment in the clinical setting. Development of educational materials for nurses to perform either of the tests would be beneficial.

Introduction

With a steady increase in the incidence of childhood cancer diagnoses since the 1950s along with simultaneous declines in mortality, long-term side effects of cancer therapy are increasingly important to proactively monitor and manage (Siegel et al., 2019).

Commonly used chemotherapy agents used in childhood cancers (e.g., platinums, vinca alkaloids) cause CIPN, often resulting in dose modifications or cessation of treatment which may increase cancer-related morbidity and mortality (Hershman et al., 2014; Kandula et al., 2016). These neurotoxic drugs cause sensory and motor nerve damage, leading to symptoms of numbness, tingling, pain in the hands/feet, and weakness which can persist far beyond the completion of chemotherapy (Gilchrist et al., 2017; Kandula et al., 2016). In addition, patients experience impaired temperature and vibration sensibility.

Although the negative effects of childhood CIPN on physical function and quality of life are well-documented, there is no ‘gold standard’ measurement tool used for research or clinical practice. Several factors impede effective CIPN assessment in the research setting (e.g., patients’ difficulty describing symptoms, providers lack of time, research assistants’ lack of confidence to assess CIPN; Lavoie Smith et al., 2014). Given the dearth of evidence regarding the incidence,

severity, trajectory of CIPN, and the patient characteristics of CIPN in children during the second year of treatment, this time period is not well-described. This lack of progress is directly related to the lack of a universally accepted comprehensive measurement tool that is reliable, valid, and clinically feasible to assess pediatric populations (Gewandter et. al., 2019; Kandula et al., 2016). Furthermore, the lack of a reliable, valid CIPN measure has made comparison among CIPN clinical trials difficult (Gewandter et. al., 2019; Kandula et al., 2016). The ability to glean the strongest items from the available peripheral neuropathy instruments and strengthen the use of common data points would allow researchers to detect phenotypic variability of CIPN at differing disease stages (i.e., early or advanced stages) and treatment stages (i.e., induction phase, consolidation, delayed intensification, maintenance phase).

Specifically, the capability to detect clinically significant changes to guide chemotherapy treatment for ALL is limited by the use of adverse event scales (e.g., The National Cancer Institute Common Terminology Criteria Adverse Events scale, World Health Organization toxicity scale, and Eastern Collaborative Oncology Group toxicity scale) as the primary outcome measure (Argyriou et al., 2012; Cavaletti, 2014; Lavoie Smith et al., 2018; Majithia et al., 2016). Adverse event scales were developed by oncology cooperative groups to document treatment-related toxicity during cancer treatment; many of these scales were endorsed by oncology organizations and were proposed for international acceptance but most never gained widespread use (Gerwandter et al., 2019).

The most commonly used adverse event scale is NCI CTCAE (Park et al., 2019). This scale has neurosensory and neuro-motor parameters with a focus on physical function. The NCI-CTCAE scale is known to lack reliability and sensitivity (Cavaletti et al., 2010; Mohrmann et al., 2017; Park et al., 2019) and often demonstrates floor effects due to the small range of values

(from 0 to 4 or 5) compared to more research focused scales for CIPN (Cavaletti et al., 2004; Cavaletti et al., 2010; Mohrmann et al., 2017; Park et al., 2019; Lavoie Smith et al., 2008). Although the scales are quick and easy to administer in a clinical setting, inter-observer disagreement is common as well (Cavaletti, 2014; Postma, Heimans, 1998).

In a large systematic review of pediatric CIPN, the incidence of any grade of VIPN using the NCI CTCAE was between 78% and 100% (Kandula et al., 2016). However, contradictory studies with incidence rates as low as 18.9% in children receiving vincristine using the NCI-CTCAE scale (Purser et al., 2014). In the past 20 years, fewer than 15 studies have evaluated the incidence of neuropathy in childhood cancer survivors (Mohrmann et al., 2017). The incidence of CIPN is related to individual agents, higher cumulative doses, higher dose intensity, shorter duration of infusion, previous neurotoxic chemotherapy, predisposing conditions (e.g., diabetes mellitus), and concurrent neurotoxic medication use (e.g., colchicine, isoniazid, hydralazine, metronidazole, lithium, dapsone, phenytoin, cimetidine, amiodarone, pyridoxine, amitriptyline) (Carlson & Ocean, 2011).

Composite scales (i.e., Total Neuropathy Scale - Pediatric Vincristine, Modified Total Neuropathy Scale – Pediatric Vincristine, Pediatric Modified Total Neuropathy Scale) for CIPN in children have recently been developed to improve reliability, validity, and ability to detect significant clinical changes (Gilchrist et al., 2014; Gilchrist et al., 2009; Lavoie Smith et al., 2013). These measures include subscales that detect sensory, sensory/motor, and motor neuropathy. The three composite scales have been used to measure CIPN in a variety of solid tumor and hematological cancer patients who received vinca alkaloids and platinum agents (Kandula et al., 2018; Gilchrist et al., 2014; Lavoie Smith et al., 2015). One scale in particular (i.e., TNS-PV) differentiates between upper and lower extremity dysfunction which

demonstrates a conceptual understanding that upper extremity neuropathy indicates more severe nerve damage compared to lower extremity nerve damage (Lavoie Smith et al., 2013). These scales include a multi-modal approach incorporating patient-reported symptoms and objective assessment with instrumental evaluation. Only three scales (i.e., Ped-mTNS, TNS©-PV, modified TNS©-PV) queries the child if they feel pain and attempts to determine the distribution of the pain. There are no specific neuropathic pain scales developed for children. When pain is the primary outcome (Gewandter et al., 2017; Lavoie Smith et al., 2013; Rao et al., 2008; Rao et al., 2007), a validated pain measure should be used, such as the Brief Pain Inventory-Short Form until a neuropathic pain scale can be developed for use in children (Atkinson et al., 2010).

Ideally, CIPN should be measured using a patient-reported outcome (PRO) survey in addition to objective measures of physical findings (e.g., deep tendon reflexes, vibration sensation). The European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire for Chemotherapy-Induced Peripheral Neuropathy (EORTC QLQ-CIPN20) and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group –Peripheral Neuropathy scale (FACT/GOG-Ntx; Calhoun et al., 2003) are examples of patient-reported outcome measures with demonstrated reliability and validity, sensitivity, and responsiveness that have been used in adult populations. To date, there are no patient-reported outcome measures for use in pediatric populations for CIPN.

The purpose of this review was to examine the literature to identify research tools that accurately measure or assess CIPN in children. Two key components of the Symptom Management Model (i.e., symptom experience, outcomes) will be used to guide this investigation. The relationship between the symptom experience component and the outcome component will be tested.

Methods

For this review, the five stages outlined by Arksey and O'Malley (2005) will be used to determine the state of the science regarding a problem of inquiry: Stage 1) Identification of the research question and eligibility criteria; Stage 2) Identification of relevant publications; Stage 3) Publication selection; Stage 4) Charting the data; and Stage 5) Collating, summarizing and reporting the results.

Stage 1 involves identifying the research questions. This review was guided by the following research questions: 1) What measures should be used with childhood cancers to assess peripheral neuropathy (clinical versus research versus adverse events)? and 2) What measures are valid and reliable for assessing vincristine-induced peripheral neuropathy in children?

Stage 2 involves identifying relevant studies to answer the research questions. A university health librarian assisted with the development of the literature search strategy and conducted the literature search in the following databases: PubMed, CINAHL, EMBASE®, and Cochrane. The search was conducted for articles published between 1968 and June 2019 that tested psychometric properties of measurement tools used to assess CIPN in children. The first documented description of CIPN in children was in 1968 (Gottschalk et al., 1968). Therefore, the search dates were selected to capture all measurement tools developed to assess CIPN in children in research studies. Controlled vocabulary (Medical Subject Headings [MeSH], CINAHL Subject Headings, and EMTREE) in addition to keywords were used. The search, conducted on July 15, 2019, was adapted for each database to include controlled vocabulary, however the search remained largely similar across databases. The search focused on four areas: 1) pediatric; 2) cancer; 3) peripheral neuropathy; and 4) measures. The key search terms were *pediatric, child, infant, pediatrics, peripheral neuropathy, peripheral nervous system diseases, tool, instrument,*

measure, and *scale.* The reference lists of relevant articles and other CIPN instrument reviews were hand-searched to identify additional articles. The full search for each database searched can be found in the appendix.

Research studies were included if they (1) involved children (age 5-18) with cancer receiving chemotherapy, (2) described the CIPN assessment tools, (3) reported psychometric properties of tools, and (4) were published in English. Studies were excluded if they (1) included adults (19 years or older), (2) did not include cancer patients, (3) were not published in English, (4) had a sample of fewer than 10 subjects, or (5) did not assess CIPN.

The search produced 257 results. Additional searching through article bibliographies was conducted. Duplicates were removed, resulting in 224 articles retrieved and abstracts reviewed. Of these 224 articles, 200 were initially excluded based on abstract and record reviews.

Stage 3 involves selection of publications. Data extraction was conducted based on the PRISMA guidelines (Hutton et al., 2015). The 24 remaining articles were then reviewed for eligibility. Two authors independently scanned the full text article to identify relevant studies that met the inclusion criteria. Questions about article inclusion were resolved through discussion among the co-authors. Of these 24 articles, nine were retained for inclusion in the review (see Figure 2.1).

Stage 4 and 5 entails charting the data and collating, summarizing, and reporting the results. A data extraction tool was used to record information from the included articles: study purpose, design, sample, tools, and psychometric properties. A second data extraction tool was used to record number of items in a measure, generalizability, reliability, criterion measure, validity, and author judgement in use of the tool. The first author independently extracted the data. Then, the data were reviewed by the second author to promote extraction accuracy.

Appraisal of Study Quality

Original research articles were identified, and the quality of each study was assessed by the QUADAS-2 assessment tool, a standardized system that assesses the unique features of the study design regarding diagnostic accuracy (Whiting et al., 2011). The tool evaluates the quality of design, including sample, reference standard, disease progression bias, verification bias, review bias, clinical bias, test execution, withdrawals, and indeterminate results. Each of the seven items in the tool were dichotomous, with 0 = yes and 1 = no. The modified rating scale allowed a range of 0 to 7 for the total score, with scores 0–3 considered a study of poor quality, 4-5 moderate quality, and 6-7 high quality. The QUADRAS-2 evaluates four domains (i.e., patient selection, index test, reference standard, flow and timing) to assess whether or not the studies were applicable to answer the review questions of the scoping review. QUADRAS-2 was evaluated independently by two researchers and differences were resolved through discussion.

Results

The aims were to 1) identify which measures should be used in childhood cancer patients to assess peripheral neuropathy for clinical versus research versus adverse events, and 2) to evaluate which measures are valid and reliable for assessing vincristine-induced peripheral neuropathy in children. The database search provided 257 records. After duplicates were removed and additional records were identified, 224 abstracts were screened. Following full text review of 24 articles, nine articles were selected (Table 2.1). Figure 2.1 presents a diagram of the article selection process.

A total of nine studies were included in the evidence synthesis evaluating a total of six CIPN tools. Seven of the nine studies utilized a modified version of the Total Neuropathy Score. Of the seven studies, four evaluated the Pediatric-modified Total Neuropathy Scale (Ped-mTNS)

in pediatric cancer patients (Gilchrist et al., 2009; Gilchrist & Tanner, 2013; Gilchrist et al., 2014; Gilchrist et al., 2017), two evaluated the Total Neuropathy Scale - Pediatric Vincristine (TNS©-PV) and the modified Total Neuropathy Scale -Pediatric Vincristine in children receiving vincristine with acute lymphocytic leukemia (ALL; Lavoie Smith et al., 2013; Lavoie Smith et al., 2015), and one evaluated the reduced Pediatric-modified Total Neuropathy Scale (rPed-mTNS) in patients with ALL (Lieber et al., 2018).

Of the six measures identified, four (67%) included combined objective and subjective scales, one (20%) included nerve conduction assessments, and one (20%) included clinician-rated scales. Four instruments (i.e., the Pediatric-modified Total Neuropathy Scale [Ped-mTNS], the reduced Pediatric-modified Total Neuropathy Scale [rPed-mTNS], the Total Neuropathy Scale – Pediatric Version [TNS©-PV], modified Total Neuropathy Scale – Pediatric Vincristine [mTNS©-PV]) have subjective and objective components to evaluate the incidence and severity of peripheral neuropathy. One instrument (the Common Terminology Criteria for Adverse Events [CTCAEv3.0/v4.0]) is subjective; relying on patient-reported or by-proxy-reported symptoms without objective data from a neurological examination. The remaining assessment (nerve conduction study [NCS]) is an objective tool that measures peripheral neuropathy based on physical examination. Three studies evaluated two or more measures (Lavoie Smith et al., 2013; Lavoie Smith et al., 2015; Lieber et al., 2018).

All of the tools described in this review have been used in research and are described in Table 2.2. The NCI-CTCAE is the most commonly used tool for adverse event reporting and clinical practice to document peripheral neuropathy however, this tools has also been used for research which is not recommended (Mohrmann et al., 2017; Park et al., 2019). The three

modified Total Neuropathy Scales have been developed for research purposes. The NCS has been used for research and clinical practice to evaluate peripheral neuropathy.

The most common examination items included a muscle strength exam (n = 4, 67%); reflex assessment (n = 4, 67%); allodynia or neuropathic pain (n = 4, 67%); numbness (n = 4) 67%); tingling (n = 4, 67%); vibration perception assessment (n = 3, 50%); motor symptoms (n = 3, 50%); autonomic symptoms (n = 2, 40%); temperature perception assessment (n = 2, 33%); pinprick perception assessment (n = 1, 20%); light touch pressure perception assessment (n = 1, 20%); and laryngeal/hoarseness (n = 1, 20%). One of the tests asked the child if they hurt and the examiner was to determine the distribution of the pain. None of the tools included a neuropathic pain item. None of the tests included joint position perception assessment or 2-point discrimination assessments. Five measures (83%) included upper and lower body examinations and five measures (83%) included the score from both sides of the body. There is high variability in the weighting of the different domains between the measures. The highest percentage of points in all tools is sensory items ranging from 20% to 60%. Next, the motor items range from 14% to 40% of points. Lastly, the sensory/motor items range from 12.5% to 20% of points and the autonomic items range from 0% to 29% of points.

Only one study described in detail the training and evaluation of competence of raters during the study (Lavoie Smith et al., 2015). Overall, five of the nine studies were rated as moderate-quality scoring between four and five on the QUADAS-2 scale with a range from 0-7 (Table 2.3). Four studies were rated as high-quality scoring between 6 and 7 on the QUADAS-2 scale. The overall incidence of CIPN reported in pediatric cancer patients ranged from 33% (Jain et al., 2013; Lieber et al., 2018) to 100% (Yildiz & Temucin, 2016).

Table 2.5 indicates the number of items, generalizability, reliability, criterion measure, validity, and the authors' recommendations for each measure. The number of items ranged from 2 (NCI CTCAE) to 8 (Ped-mTNS). Four of the tools were generalizable to all phenotypes of CIPN in children. Two tools were not generalizable and have only been tested in children receiving vincristine. The highest Cronbach's α was 0.84 (modified TNS©-PV). Five of the tools had a high correlation with a criterion measure and four of the tools had high validity. Two tools were deemed poor to use in children with CIPN due to poor psychometric properties (NCI CTCAE) or due to length of the test, expense, and discomfort for the child (NCS). One tool was rated as good for use in CIPN in children and one tool was rated as good for use in children receiving vincristine.

Review of Measurement Tools

There are several measurement tools used to assess peripheral neuropathy in children. The psychometric properties of each test will be discussed including the appropriate use of each (e.g., clinical or research). Only some of the tools are optimal for research purposes.

The National Cancer Institute Common Terminology Criteria for Adverse Events

The NCI-CTCAE is a grading scale developed in 1983 by the Cooperative Oncology groups in North America and Canada to assist clinicians in recognizing and documenting adverse effects of chemotherapy, including motor and sensory neuropathy (Trotti et al., 2003). The purpose of the NCI-CTCAE versions 2.0, 3.0, or 4.0 (Trotti et al., 2003) grading scale is to standardize the assessment and reporting of adverse events to allow clinicians to decide whether a specific chemotherapy has benefit over the potential toxicities that may occur (Miller et al., 1981). The NCI-CTCAE scale allows for gross assessment of CIPN through subjective and objective parameters (sensory, motor, and reflexes). Toxicity is graded from 0 to 5, with 0

indicating no toxicity and 5 representing paralysis for version 2.0 and death for version 3.0 (Cavaletti & Marmiroli, 2010). The endpoints for the earlier versions of the NCI-CTCAE are extreme. The latest version (4.0) includes subjective and objective sensory and motor parameters that are conflated to score sensory CIPN and motor CIPN with more severe symptoms earning a higher score (Cavaletti & Marmiroli, 2010). Oncologists use this scale in the practice setting on a regular basis due to its ease of use and familiarity.

Research evidence supports the NCI-CTCAE's motor scale construct validity based on moderate correlations between strength testing on the ped-mTNS and the motor portion of the CTCAE (Gilchrist et al., 2014). In addition, there is a moderate association between the combined motor symptom and strength scores on the ped-mTNS and motor neuropathy on the CTCAE ($r_s = 0.32$, $p = 0.01$; Gilchrist et al., 2014).

The NCI-CTCAE combined motor and sensory scale showed higher scores in patients at risk for CIPN with higher cumulative doses ($p = 0.02$) and comorbid conditions ($p = 0.001$); however, construct validity was not supported in patients with higher M^2 chemotherapy doses (Lavoie Smith et al., 2011). There was no statistically significant association found between the area under the curve and the NCI-CTCAE (Lavoie Smith et al., 2013). Thus, there is a lack of evidence to support construct validity in the sensory scale. No single item measuring sensory signs or symptoms on the ped-mTNS correlated with the CTCAE (Gilchrist et al., 2014).

The NCI-CTCAE has five generalized grading categories and lacks sensitivity (Lavoie Smith et al., 2008). The NCI-CTCAE scale also lacks responsiveness due to significant floor effects and does not have adequate reliability (Gilchrist et al., 2014; Lavoie Smith et al., 2013). The NCI-CTCAE scores were low (0-2) for 98% of the sample (Lavoie Smith et al., 2013). The NCI-CTCAE demonstrated only a 46% inter-observer agreement (Postma et al., 1998). This

adverse events scale can be used for reporting toxicities but should not be used to monitor CIPN and should not be used for research purposes. In summary, the NCI-CTCAE is appropriate for reporting treatment-related toxicities however, this tool is not well suited for research purposes.

Pediatric Modified Total Neuropathy Score (Ped-m TNS)

The Ped-mTNS was developed by Gilchrist et al. (2009) for use in school age children for research purposes. The scale has eight items including subjective sensory, motor, and autonomic components, light touch sensibility, pin sensibility, vibration sensibility, strength test, and deep tendon reflexes (Gilchrist et al., 2009). The scale is scored on a 0 to 4 likert type scale with a range from 0 to 32. A value of 5 or greater indicates neuropathy and a higher score indicates more severe neuropathy. The test takes less than 10 minutes. Feasibility was determined when 100% of children age 5 to 18 were able to complete the assessment.

Internal consistency reliability was evaluated with a Cronbach's alpha coefficient of 0.76 (Gilchrist & Tanner, 2013). The test-retest reliability was good, with an intra-class correlation coefficient (ICC) of 0.99 (Gilchrist & Tanner, 2013). The inter-rater reliability was evaluated with children ages 5 to 18 years old, and the total scale score had an ICC of 0.98 (Gilchrist & Tanner, 2013). There was no age effect detected for this measure.

Construct validity was shown to have higher scores among children undergoing chemotherapy compared to chemotherapy-naïve patients (Gilchrist & Tanner, 2013). There was no correlation with the Ped-mTNS and children receiving higher cumulative dose of vincristine (Gilchrist & Tanner, 2013). This measure does not appear to have any floor or ceiling effects and has a large range of scores indicating good variability of the measurement tool (Gilchrist & Tanner, 2013). The Ped-m TNS did not correlate with the NCI-CTCAE scale (Gilchrist et al., 2014). This is may be the result of the construct of sensory not being validated or supported in

the NCI CTCAE. No single item measuring sensory signs or symptoms on the ped-mTNS correlated with the CTCAE. There was no correlation between the combined sensory item scores and the CTCAE sensory score or between motor symptoms on the ped-mTNS and the motor portion of the CTCAE. There was a moderate association between strength testing on the ped-mTNS and the motor portion of the CTCAE and a moderate association between the combined motor symptom and strength scores on the ped-mTNS and motor neuropathy on the CTCAE ($r_s = 0.32$, $p = 0.01$). This measure does not include autonomic components and does not evaluate neuropathic pain; however, it is easy to administer and does not require specialized providers or specialized equipment. This test has good generalizability to pediatric cancer populations and strong psychometric properties. The one drawback to this measurement tool is the pinprick item which could cause psychological distress in young children who are already vulnerable after multiple procedures and treatment. This tool would be appropriate for use in adolescents because they can understand the importance of pinprick testing to evaluate their peripheral neuropathy. The Ped-mTNS would not be recommended for use in children.

Reduced Pediatric Modified Total Neuropathy Score

The reduced Ped-m TNS (rPed-mTNS) is a composite scale for the assessment of CIPN developed by Lieber et al. (2018) for the purpose of research in school-age children. The scale comprises five items: subjective sensory, motor, and autonomic components, a strength test, and deep tendon reflexes (Lieber et al., 2018). Each item is scored on a 0 to 4 scale, with higher cumulative scores indicating worsening neuropathy. The maximum score for the test is 20. A score of 4 or greater corresponds with CIPN. This cut point was based on finding that 5% of normal pediatric controls have a ped-mTNS (a different TNS© variant) score of four or higher, and no normal controls had scores ≥ 5 (Gilchrist & Tanner, 2013; Lavoie Smith et al., 2013).

The incidence of CIPN in children with ALL was 33% according to the rPed-mTNS. Compared to nerve conduction studies, the rPed-mTNS had low sensitivity (29%; Lieber et al., 2018). There were no correlations identified with risk factors such as age, gender, or time since last chemotherapy treatment. There is no evaluation of reliability or responsiveness of the scale described to date. Based on the studies to date, this tool would not be recommended for clinical or research use. Further psychometric testing would be helpful to validate this tool.

Nerve Conduction Studies

Nerve conduction studies (NCS) were developed for clinical use to measure nerve conduction velocity (i.e., speed of electrical impulses through a nerve), amplitude, and negative peak duration (NPD) of compound muscle action potentials (CMAP) for motor nerves using surface electrodes (Yildi & Temucin, 2016). A reduced nerve conduction velocity, measured in meters per second, identifies neuropathy involving axon or myelin sheath injury within the nerve. All values of the NCS are matched with age-adjusted reference values to determine if CIPN is present. For example, children under the age of five are determined to have CIPN when the conduction velocity is less than 21 m/s in the plantar nerve or less than 20 m/s in the post tibial nerve (Liveson, 1992). NCS are considered the most accurate tool for evaluating large fiber neuropathy (Lieber et al., 2018). The NCS takes approximately 30 to 45 minutes to complete and can be painful to children.

Based on NCS, the incidence of CIPN was 100% in children with ALL post-treatment (Yildiz & Temucin, 2016). The first factor analysis for CMAP amplitude revealed that the first factor (motor amplitude factor) is capable of explaining 70.8% of the variance in CMAP amplitude. (Yildiz & Temucin, 2016). The second factor analysis for CMAP NPD revealed that the first factor (motor duration factor) is capable of explaining 70.8% of the variance for CMAP

duration parameters (Yildiz & Temucin, 2016). A result greater than 70% satisfies the criterion of explaining the total variance. The patient group had a significant decrease in CMAP amplitudes compared to controls. NCS are time consuming, expensive, and can be painful to the child. This measurement would be not recommended for screening or monitoring CIPN. The barriers are also too significant for use in research.

Total Neuropathy Score Pediatric Vincristine (TNS©-PV) and Modified Total Neuropathy Score Pediatric Vincristine (mTNS©-PV)

The TNS©-PV was developed by Lavoie Smith et al. (2013) for research purposes to use in children diagnosed with acute lymphocytic leukemia who were receiving vincristine. The measure quantifies subjective numbness, tingling, neuropathic pain, temperature sensibility, vibration sensibility, and constipation, and it objectively measures muscle strength, deep tendon reflexes, and vocal cord function. Each item is scored on a 0 to 4 scale, with a range of 0 to 28 and higher cumulative scores indicating worsening neuropathy. A value of 4 or more indicates neuropathy. This assessment tool replaced the pinprick testing with temperature sensation out of concern for discomfort in the pediatric population. Alternative scoring was developed to differentiate signs and symptoms reported or tested in the hands and feet and was known as Form B. For Form A scoring, patients with neuropathy in their hands or feet can receive the same score. Lavoie Smith et al. (2013) developed Form B based on the view that neuropathy in the hands and feet should be scored higher or more severe than a patient just having neuropathy in their feet. However, there was not a statistically significant difference between Form A and Form B scoring. When comparing Form B to Form A scores, Form B mean and standard deviation scores were higher, indicating more sensitivity in detecting vincristine-induced peripheral

neuropathy. Feasibility was determined when 100% of children age 6 to 18 were able to complete the assessment.

Item-to-item correlations were moderately strong (*r* range = 0.51 – 0.87) between paresthesias, numbness, neuropathic pain items, and the worst symptom item. Statistically significant correlations were found for most item (*P* range = .01 - .05) however, the strength of the correlations was low (Lavoie Smith et al., 2013). The laryngeal and autonomic (constipation) items had suboptimal item-to-item correlations and most likely are not internally consistent. Internal consistency reliability was supported with a Cronbach's α coefficient of 0.68; however, after removing two items (laryngeal and autonomic components), this increased to 0.84 (Lavoie Smith et al., 2013). This reduced tool is called the Modified TNS©-PV. Inter-rater reliability was acceptable for nearly all items of the TNS©-PV and improved with Form B. Scores for the TNS©-PV from trained raters correlated with TNS©-PV scores from neurologists (K_w range = 0.54 – 0.99; Lavoie Smith et al., 2013).

Construct validity was evaluated based on moderate correlations with cumulative dosage (*r* = 0.53) and vincristine area under the curve (*r* = 0.41) (Smith et al., 2013). Convergent validity is evidenced by moderately strong correlations between the TNS©-PV and the NCI CTCAE (*r* range = 0.48 – 0.52; Lavoie Smith et al., 2013). The TNS©-PV is responsive to change over time. The feasibility was determined for children 6 years of age and older. This measure does address chemotherapy-related pain, and it separates the hands and feet to show neuropathy progression. This measure is the most comprehensive, valid, and reliable tool for use in school-age children.

Discussion

The incidence and prognosis of childhood CIPN have been shown to differ from that of adult CIPN, which indicates a need for a pediatric-specific CIPN assessment tools (Howard et al., 2014; Lavoie Smith et al., 2015). Multiple tools for assessing CIPN have been validated in school-age children; however, there are no validated tools for use with children younger than 5 years of age.

The most widely used adverse event scale, the NCI CTCAE, was not designed for research purposes to measure CIPN, but instead to guide gross assessment of CIPN. The two-item scale is quick, easy to administer, and helpful for screening children at risk for CIPN; however, the severity and variability of CIPN cannot be determined, and inter-observer disagreement is common. With a range of 0 (asymptomatic) to 5 (death), the scale has been criticized for its limited capability to detect clinically significant change nor is it responsive to change over time (Cavaletti et al., 2010; Kuroi et al., 2009; Postma et al., 1998). Terms such as mild, moderate, and severe are used to describe CIPN; however, the adverse event scales do not operationalize the categories to make them unambiguous (Cavaletti et al., 2013). This lack of clarity leads to various interpretations by researchers and clinicians (Park et al., 2019). The adverse event scale also has the limitation of floor effects because most providers rate patients between 0 and 2 (Cavaletti et al., 2004; Lavoie Smith et al., 2008; Park et al., 2019). While this tool may be adequate for adverse event reporting, it should not be used for research or clinical use to measure CIPN in children.

Nerve conduction studies are time-consuming, expensive, personnel-intensive, and not child-friendly. The NCS was developed for use in the clinical and research settings however, it is lengthy to administer and measures large fiber nerve damage. Small nerve fibers are not assessed

at all if NCS is used. This test can also be painful and with such strong evidence regarding the psychosocial effects of cancer on children, minimizing painful testing would seem prudent thus this tool would not be recommended for research or clinical use (Khalifa et al., 2014).

The most reliable and reproducible tools of peripheral nerve damage are measured through composite subjective and objective items that measure sensory and motor components. The development of a gold standard test will need to include objective and subjective components. The Ped-m TNS has been demonstrated to be a valid and reliable tool that is generalizable to pediatric cancer patients receiving a variety of neurotoxic agents. This tool has one item assessing pain in the child. It is applicable for research and clinical use. The one drawback of this tool is the pinprick item which could traumatize the child.

The TNS©-PV has a less than optimal Cronbach's α of 0.68 however by eliminating 2 item (i.e., constipation and laryngeal/hoarseness) this reliability can be improved to 0.84. This tool is renamed the modified TNS©-PV and can be used to measure children receiving vincristine in less than 10 minutes. This tool has not been tested in children receiving other neurotoxic chemotherapy agents thus may not be generalizable. The modified TNS©-PV, which also has one item assessing neuropathic pain, is the most valid and reliable measures for use in research for prevention and treatment trials in school-age children and in the clinical setting as well. The TNS©-PV would be optimal because the Ped-mTNS involves a pinprick during the physical examination. This can be traumatic for young children.

In summary, the NCI-CTCAE should only be used for reporting adverse events. The NCS may be useful to diagnose the type of neuropathy however, most often, in children, the reason for neuropathy development is evident. The Ped-m TNS is useful as a research and clinical tool in children receiving neurotoxic chemotherapy and in more generalizable than the

TNS©-PV. However one of the items is a pinprick test which can cause psychological distress to young children. The answer to dissertation aim 1 is that the modified TNS©-PV is optimal as a research and clinical tool to screen and monitor children for peripheral neuropathy who are receiving neurotoxic medications.

Limitations

Some limitations can be drawn from this scoping review. This review only included articles published in English, which could lead to a publication bias. The tools of this scoping review were limited to measuring chemotherapy-induced peripheral neuropathy thus these findings could not be applied to other types of peripheral neuropathies including diabetes or HIV treatment.

Conclusion

The lack of available and suitable tools to measure CIPN in pediatric populations is apparent. Clinical assessment tools are needed as well as research appropriate measures. The gaps in the literature include being able to screen for CIPN in young children. The clinician asking subjective questions to a young child would need to determine whether the child is able to comprehend the vocabulary and concept being assessed (e.g., numbness, tingling, pain). Many researchers and providers depend on the caregiver to answer the questions if the child is unable to do so however, research has shown that caregivers and providers often underestimate the symptoms a child is experiencing (Silva & Barros, 2013). Thus this may not accurately measure CIPN in young children.

Future research needs to focus on the development of a ‘gold standard’ tool for children receiving chemotherapy. A standard measurement for research will allow for comparisons across studies and facilitate the advancement of science in this understudied area.

APPENDIX

Figure 2.1

PRISMA Search Strategy Diagram

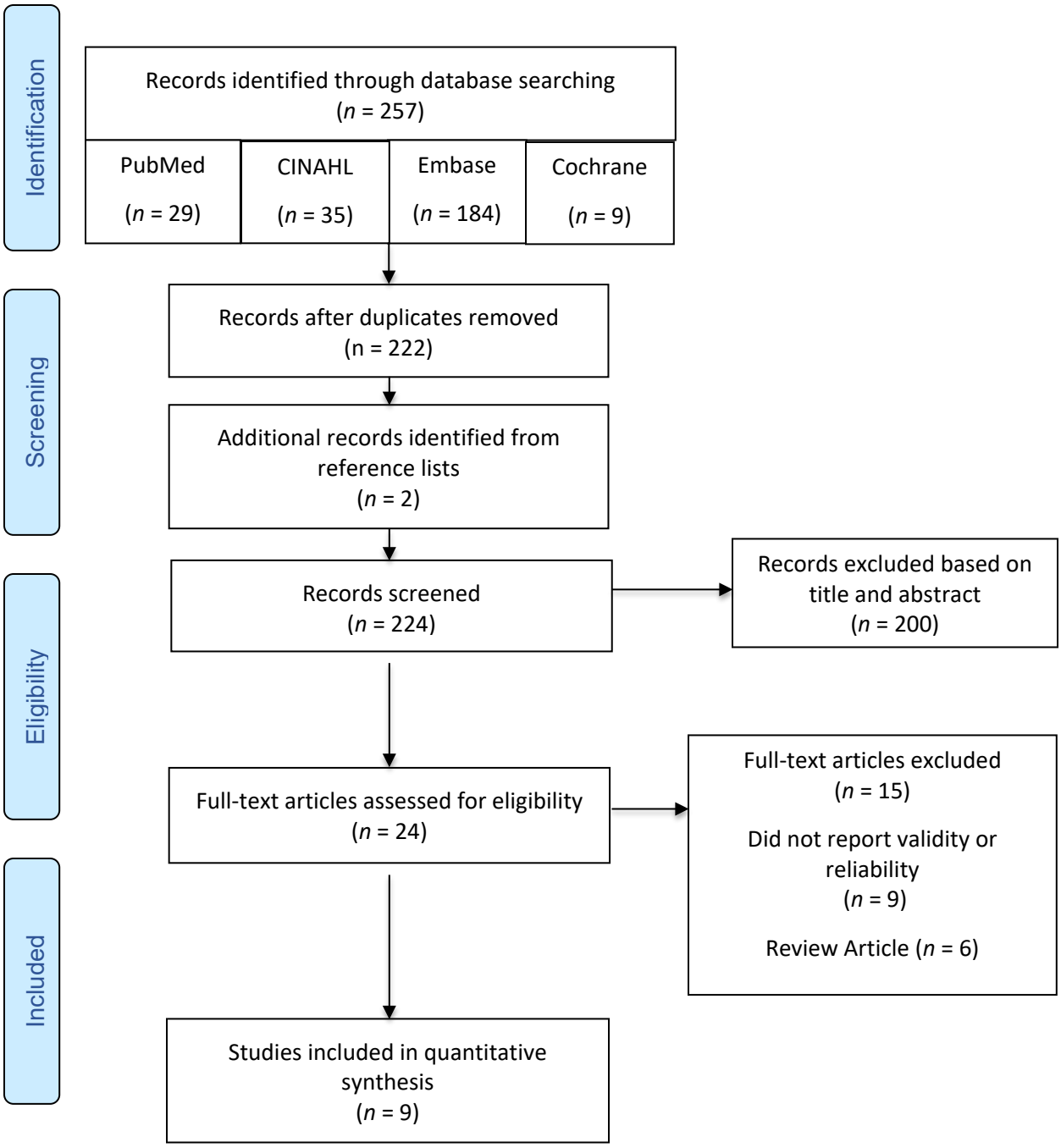

Table 2.1

Study Subjects and Characteristics

Study	Quality score	Design	Age of participants	Number of participants	Tools	Number of assessments	Results
Gilchrist et al. (2009)	5	Pilot study, cancer patients Convenience sampling	5-18 years	*N* = 20	Ped-mTNS, NCI-CTCAE v3.0	1 assessment collected by single examiner	CIPN incidence was 75% according to the Ped-mTNS. Incidence of sensory CIPN 60%. Incidence of motor CIPN 55% Mean score of the Ped-mTNS 6.1 (SD, 3.8); scoring range 0-24 with score 0-4 being negative test Moderate correlation was found between motor symptoms and strength (0.554, *P* < .05) Motor symptoms and sensory symptoms (0.487, *P* = .05) Motor symptoms and vibration sensitivity (0.613, *P* = .1) Motor symptoms and deep tendon reflexes (0.456, *P* = .17) Motor symptoms and pin and vibration sensibility (0.539, *P* < .05) No correlation found between pin and vibrations sensibility Feasibility of the Ped-mTNS determined by 100% of children ages 5-18 completing assessment

Table 2.1 (cont'd)

Study	Quality score	Design	Age of participants	Number of participants	Tools	Number of assessments	Results
Gilchrist & Tanner (2013)	5	Descriptive, cancer patients Convenience sampling	5-18 years	*N* = 82	Ped-mTNS, Bruininks-Oseretsky Test of Motor Proficiency version 2 (BOT-2)	1 assessment 10 patients were retested 1 hour later by a second trained physical therapist researcher	CIPN incidence 85% according to the Ped-mTNS; sensory CIPN (27%), motor CIPN (49%), and autonomic CIPN (37%) were reported No correlation was found with cumulative dose of vincristine and neuropathy score No correlation with cumulative vincristine dose and balance a manual dexterity Cancer patients had worse Ped-mTNS scores (8.7 $\pm$ 4.2; range 2-18) than controls (1.4 $\pm$ 0.9; range 0-4) Neuropathy measure found negative associations with balance ($r_s = 0.626$, $P < .001$) and manual dexterity Cronbach's $\alpha = 0.76$ Test-retest reliability ICC = 0.99 (95% CI 0.96 – 0.99) Inter-rater reliability ICC = 0.98 (95% CI 0.95 – 0.99) Children with cancer scored significantly lower on balance manual dexterity compared to controls

Table 2.1 (cont'd)

Study	Quality score	Design	Age of participants	Number of participants	Tools	Number of assessments	Results
Gilchrist et al. (2014)	6	Descriptive, cancer patients Convenience sampling	5-18 years	*N* = 60	Ped-mTNS NCI-CTCAE v3.0	1 assessment completed by research assistant and oncologist	CIPN incidence was 91% according to the Ped-mTNS No correlation was found between Ped-mTNS scores and combined sensory and motor CTCAE scores Floor effects were found on the CTCAE compared to the Ped-mTNS 40% of children had unidentified light touch abnormalities based on CTCAE compared to Ped-mTNS No single item measuring sensory signs or symptoms on the Ped-mTNS correlated with CTCAE No correlation between the combined sensory item scores and the CTCAE sensory scores No correlation between motor symptoms on Ped-mTNS and motor portion of CTCAE Moderate association between strength testing on Ped-mTNS and motor portion of CTCAE Moderate association between the combined motor symptom and strength scores on the Ped-mTNS and motor neuropathy on CTCAE (r_s = 0.32, *P* = .01)
Gilchrist et al. (2017)	5	Descriptive, cancer patients Convenience sampling	5-18 years	*N* = 65	Ped-mTNS Bruininks-Oseretsky Test of Motor Proficiency version 2 (BOT-2)	1 assessment while on treatment, 1 assessment 3 months after treatment, and 1 assessment 6 months after treatment	While on treatment and 6 months post-treatment, moderate negative association between balance score and Ped-mTNS were found, respectively (r_s = -0.34, *P* = .005) (r_s = -0.31, *P* = .01). Only sensory symptoms (numbness, paresthesias, distal pain) (r_s = -0.29, *P* = .02) and vibration sensibility (r_s = 0.26, *P* = .04) were significantly associated
Jain et al. (2014)	6	Cross-sectional study Children diagnosed with ALL	5-18 years	*N* = 80	NCS rTNS	1 assessment at follow-up oncology visit post treatment	CIPN incidence was 33% based on NCS CIPN incidence was 33% based on rTNS Score of $\geq$ 1 on rTNS correlated with nerve pathology This study was not adequately powered to detect associations between risk factors in children with ALL and occurrence of CIPN

Table 2.1 (cont'd)

Study	Quality score	Design	Age of participants	Number of participants	Tools	Number of assessments	Results
Lavoie et al. (2013)	6	Descriptive, acute lymphoblastic leukemia patients	1-19 years	*N* = 65	TNS©-PV, Modified TNS©-PV, NCI-CTCAE v4.0, Balis Pediatric Scale of Peripheral Neuropathy, Tuning Fork FACES	1 assessment at baseline and prior to each vincristine infusion up to 15 weeks of treatment	Cronbach's α for 7-item TNS©-PV was 0.68 Cronbach's α for modified 5-item TNS©-PV was 0.84 (laryngeal and autonomic items were dropped) Inter-rater reliability was moderately strong (K_w = 0.54 – 0.99) Inter-rater reliability was better when Form B was used Responsive to change over time; reflex, temperature, and vibration items were most responsive (effect size = 0.31 – 0.66, *P* = .006 to < .0001) TNS©-PV Form A correlation with CTCAE and Balis scores (*r* = 0.48 – 0.52, *P* = .01) TNS©-PV was not highly correlated with FACES (*r* = 0.20, *P* = .01) TNS©-PV had moderately strong correlation with vincristine cumulative dosage (*r* = 0.53, *P* = .01) CTCAE shows change over time < 50% of 3-year-olds completed subjective symptom information Feasible to use in children 6 years and older
Lavoie Smith et al. (2015)	5	Descriptive, acute lymphoblastic leukemia patients	1-19 years	*N* = 109	TNS©-PV NCI-CTCAE v4.0 Modified Balis Pediatric Scale of Peripheral Neuropathy		CIPN incidence as measured by TNS©-PV was 78%. TNS©-PV scores were positively associated with age (*r* = 0.31, *P* < .0001) No significant differences were associated with race or gender TNS©-PV diagnosed more children with VIPN compared to CTCAE

Table 2.1 (cont'd)

Study	Quality score	Design	Age of participants	Number of participants	Tools	Number of assessments	Results
Lieber et al. (2018)	6	Cross-sectional, bicentric, observational study of leukemia patients	6-18 years	*N* = 46	QST rPed-mTNS NCS	1 assessment 3 months after last treatment	33% of patients diagnosed with peripheral neuropathy using rPed-mTNS compared to 15% using NCS rPed-mTNS correlated 100% with QST testing for pain sensitization rPed-mTNS had low sensitivity (29%) for large fiber function measured by slowed NCS No correlation was found with known risk factors of age, gender, and time interval after completion of chemotherapy using rPed-mTNS, NCS, or QST testing
Yildiz & Temucin (2016)	4	Retrospective descriptive study Subjects included childhood cancer patients receiving vincristine	Mean 7.2 years	*N* = 25	NCS	Chart review of NCS and neurological symptoms Compared with control group of normal children	CIPN incidence 100%. First factor analysis for CMAP amplitude revealed first factor (motor amplitude factor) explained 70.8% variance in CMAP amplitude Second factor analysis for CMAP NPD revealed first factor (motor duration factor) explained 70.8% variance for CMAP duration parameters (> 70% satisfies criterion of explaining total variance) Patient group had significant decrease in CMAP amplitudes compared to control group Significant increase in distal CMAP NPD in patient group compared to control group

Note. Abbreviations: ALL, acute lymphocytic leukemia; BOT-2, Bruininks-Oseretsky Test of Motor Proficiency version 2; BPI-SF, Brief Pain Inventory;-Short Form CIPN, chemotherapy-induced peripheral neuropathy; CMAP, compound muscle action potential; CMAP NPD, compound muscle action potential negative peak duration; NCI-CTCAE, National Cancer Institute Common Terminology Criteria Adverse Effects Scale; NCS, nerve conduction study; NRS, numeric rating scale; ped-mTNS, pediatric-modified Total Neuropathy Scale; PRO, patient-reported outcome measure, QST, quantitative sensory testing.

Table 2.2

Pediatric Chemotherapy-Induced Peripheral Neuropathy Screening/Assessment Tools

Tool	Brief Description	Proposed Target Population	Advantages/Disadvantages
Common Terminology Criteria for Adverse Events v4.0 (NCI-CTCAE)	Grading scale developed by the National Cancer Institute to classify the severity of adverse events in patients receiving chemotherapy Detects motor and sensory neuropathy ● Grade 1 – asymptomatic or symptoms ● Grade 2 – moderate symptoms; limiting instrumental ADL ● Grade 3 – severe symptoms; limiting self-care ADL ● Grade 4 – life-threatening consequences; urgent intervention indicated ● Grade 5 – death	Can be used in all ages of cancer patients	Floor effects detected There is overlap of grade 2 and grade 3 CTC scores CTC Motor scores were significantly higher than TNS scores and did not detect motor neuropathy diagnosed by the TNS but more likely physical fatigue
Pediatric-modified Total Neuropathy Score (ped-mTNS)	Combined subjective and objective scale ● 3 symptom questions ● 5 physical examination signs Detects sensory, motor, and autonomic neuropathy Eight items scored 0 to 4 on Likert-type scale Total score can range from 0 to 32 Score of 5 or greater indicates neuropathy Higher score indicates more severe neuropathy	Children 5-18 years of age with CIPN	Good reliability and internal consistency Good for screening and assessment Not as sensitive to change over time Clinical significance of scores is unclear No floor or ceiling effects detected Does not measure children less than 5 years of age
Reduced Pediatric-modified Total Neuropathy Score (rPed-mTNS)	Combined subjective and objective scale ● 3 symptom questions ● 2 physical exam signs Detects sensory and motor neuropathy Five items scored 0 to 4 on Likert-type scale Total score can range from 0 to 20 Score of 4 or greater indicates neuropathy	Children 5-18 years of age with CIPN	Poor sensitivity for detecting CIPN Only one study investigating psychometric testing. No evidence to support that this tool is responsive to change

Table 2.2 (cont'd)

Total Neuropathy Score – Pediatric Vincristine (TNS©-PV)	Combined subjective and objective scale Detects sensory, motor, and autonomic neuropathy 7 items scored 0 to 4 on Likert-type scale Total scores can range from 0 to 28 Score of 4 or higher indicates neuropathy Higher score indicates more severe neuropathy	School-age children with vincristine-induced peripheral neuropathy	Good reliability and sensitive to change over time Takes < 10 minutes to complete. Sensory symptoms are not reported individually (numbness, tingling, pain)
Modified Total Neuropathy – Pediatric Vincristine (mTNS©-PV)	Combined subjective and objective scale Detects sensory, sensory/motor, and motor neuropathy 5 items scored 0 to 4 on Likert-type scale Total scores can range from 0 to 20 Higher score indicates more severe neuropathy	School-age children with vincristine-induced peripheral neuropathy	Good reliability and sensitive to change over time Takes < 10 minutes to complete. Sensory symptoms are not reported individually (numbness, tingling, pain)
Nerve Conduction Study (NCS)	Nerve conduction velocity to measure large fiber neuropathy with surface electrodes Measures motor and autonomic neuropathy	Children 6-18 years of age with CIPN	Test takes 30-45 minutes to complete; Can be painful.

Note. Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; NCI-CTCAE, National Cancer Institute Common Terminology Criteria Adverse Effects Scale; NCS, nerve conduction study; NRS, numeric rating scale; PRO, patient-reported outcome measure; TNS, Total Neuropathy Score; VAS, visual aalog scale; VDS, visual descriptive scale.

Table 2.3

QUADAS-2 Evidence Table

Author	Year	Risk of Bias				Applicability Concerns			Score	Quality of the Study
		Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard		
Gilchrist et al.	2009	1	0	0	1	1	1	1	5	Moderate
Gilchrist & Tanner	2013	0	0	1	1	1	1	1	5	Moderate
Gilchrist et al.	2014	1	1	0	1	1	1	1	6	High
Gilchrist et al.	2017	0	0	1	1	1	1	1	5	Moderate
Lavoie Smith et al.	2013	1	1	0	1	1	1	1	6	High
Lavoie Smith et al.	2015	1	0	0	1	1	1	1	5	Moderate
Lieber et al.	2018	1	0	1	1	1	1	1	6	High
Jain et al.	2014	1	0	1	1	1	1	1	6	High
Yildiz & Temucin	2016	0	0	1	0	1	1	1	4	Moderate

Note. Abbreviations: QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies version, 0 = yes, 1 = no

Table 2.4

Comparison of the Pediatric Total Neuropathy Scales

Scale Item	TNS©-PV	Modified TNS©-PV	Ped-mTNS	rPed-mTNS
Numbness, tingling, or neuropathic pain	x	x	x	x
Motor symptoms			x	x
Autonomic symptoms	x		x	x
Pin sensation exam			x	
Vibration sensibility	x	x	x	
Temperature sensibility	x	x		
Light touch sensation			x	
Strength exam	x	x	x	x
DTR	x	x	x	x
Laryngeal/hoarseness	x			
Nerve conduction				

Note. Abbreviations: TNS©-PV, Total Neuropathy Score – Pediatric Vincristine; Ped-mTNS, Pediatric modified Total Neuropathy Scale; rPed-mTNS, reduced Pediatric modified Total Neuropathy Scale; DTR, Deep Tendon Reflexes

Table 2.5

Measures: Chemotherapy-Induced Peripheral Neuropathy

Measures	Number of Items	Generalizability	Reliability	Criterion Measure	Validity	Judgement
Modified TNS©-PV	5	no	good	high	high	very good
TNS©-PV	7	no	questionable	high	high	good
Ped-mTNS	8	yes	acceptable	high	high	good
rPed-mTNS	5	yes	unknown	high	mod	poor
NCS	3	yes	good	high	high	moderate
NCI-CTCAE	2	yes	poor	moderate	moderate	poor

Note. Abbreviations: NCI-CTCAE, National Cancer Institute Common Terminology Criteria Adverse Effects Scale; Ped-mTNS, Pediatric modified Total Neuropathy Score; rPed-mTNS, reduced Pediatric modified Total Neuropathy Score; NCS, nerve conduction study; TNS©-PV, Total Neuropathy Score – Pediatric Vincristine.

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CHAPTER 3: EVALUATING PERIPHERAL NEUROPATHY IN CHILDHOOD CANCER PATIENTS DURING YEAR TWO OF TREATMENT

Abstract

Survival of children diagnosed with acute lymphocytic leukemia (ALL) has improved significantly over recent decades secondary to treatment advances, thus survivorship has become a major focus. Vincristine-induced peripheral neuropathy (VIPN) is a common toxicity resulting from ALL treatment that can affect a child's quality of life and functional status in long-term survivorship; however, studies analyzing the vincristine impact on the peripheral nervous system over time in children are scarce. Although it is recognized that children experience motor, sensorimotor, and sensory neuropathy during the first year of Vincristine treatment, limited research has examined the impact of second year ALL treatment on the progression of peripheral neuropathy.

The retrospective study characterizes VIPN progression and relative contribution of each pathway during the second year of ALL treatment in a sample of 77 children (289 assessments). Guided by the Symptom Management Model, the relationship between symptom experience and outcomes were tested.

A secondary data set was completed with data obtained from a de-identified dataset derived from pediatric patients (ages 5-18) with cancer recruited from the four comprehensive cancer centers. Using Friedman's Test and Wilcoxon Test, the average mTNS©-PV score was used to determine the severity of VIPN at selected time points among the patients, as well as determining if there are significant differences in average mTNS©-PV scores at different time points. In addition, the type of nerve pathway was identified (sensory - both temperature and

vibration sensibilities, motor, and/or sensory/motor) that contributed the most to a higher VIPN score at 12, 15, 18, 21, and 24 months according to the mTNS©-PV subscales.

Based on modified Total Neuropathy Score - Pediatric Vincristine (mTNS©-PV) scores, 56% (n = 43) of the children exhibited VIPN among the five time points during year two of ALL treatment. A nonparametric Friedman's test of differences among repeated measures was conducted for the mean mTNS©-PV score at each time point and rendered a Chi-square value of 14.44 which was significant ($p < .006$) rejecting the null hypothesis that the mean scores of the mTNS©-PV were equal at 12, 15, 18, 21 and 24 months. The Wilcoxon test evaluated the mean mTNS©-PV score for each time point and there was no significant difference between month 12 and month 24 ($p = .456$). There was a statistically significant difference between 21 and 24 months ($p < .001$). Sensory/motor pathway (reduced deep tendon reflexes) had the highest severity during year two.

Study findings provide evidence that VIPN is a persistent and pervasive symptom that does not resolve during the second year of treatment. VIPN remains stable throughout year 2 of ALL treatment. Interventions should be tested to reduce VIPN beginning in year one and continued during year two of ALL treatment. Based on these findings in which sensory/motor is most affected, interventions need to focus on sensory and motor pathways in order to affect the sensory/motor pathway. In addition, due to the identified sensory deficits in the hands and feet during year two, safety interventions should be implemented for children to prevent accidental injury.

Introduction

Acute lymphocytic leukemia (ALL), the most common childhood cancer, accounts for approximately one-third of all pediatric cancers in children 0 to 14 years of age (Siegel et al.,

2019). As a result of advances in treatment, patients diagnosed with ALL have a five-year overall survival rate exceeding 85% (Siegel et al., 2019). ALL treatment is guided by standardized treatment protocols consisting of multi-drug regimens (i.e., vincristine, dexamethasone, pegaspargase, methotrexate, cytarabine) divided into treatment phases (i.e., induction, consolidation, interim maintenance, delayed intensification, and maintenance), which usually last two years for girls and three years for boys (Demidowicz et al., 2019; National Comprehensive Cancer Network, 2016; Salzer et al., 2010). Children with ALL are placed in risk groups (i.e., standard, intermediate, high, very high) based on presenting clinical and laboratory features with more intensive treatment given to higher risk patients. Patients of older age, higher white blood cell count, or with testicular involvement are considered very high risk. Treatment regimens are based on risk group; many of which are developed by the Children's Oncology Group Treatment trials (Koh et al., 2018). In Table 3.1, the various ALL protocols stratified by risk group are shown with eligibility criteria. Regardless of the protocol, a child receives vincristine dosing at 1.5 mg/m^2.

Unfortunately, many children have serious side effects and lasting sequelae from treatment, including vincristine-induced peripheral neuropathy (VIPN; Freyer et al., 2011; Lavoie Smith et al., 2015; Lavoie Smith, Li, et al., 2013; Legha, 1986; Nama et al., 2020). Vincristine, the mainstay of therapy, causes sensory and motor peripheral nerve damage that progresses from distal to proximal nerves starting in the lower extremities. This is often described as a stocking and glove distribution of peripheral neuropathy as shown in Figure 3.1. Common symptoms include numbness, tingling, neuropathic pain, decreased vibration and temperature sensibility, loss of deep tendon reflexes (DTRs), and decreased muscle strength (Lavoie Smith et al., 2015; Windebank & Grisold, 2008). Treatment-related nerve damage

manifests as foot drop, altered balance and coordination, and impaired gait patterns leading to physical limitations (Gocha Marchese et al., 2003; Hoffman et al., 2013; Nama et al., 2020; Ness et al., 2009; Wright et al., 2017) and an increased risk of falling (Bao et al., 2016; Kolb et al., 2016). The first clinical sign of VIPN, which develops within a week of initiating treatment, is the reduction or loss of DTRs (Argyriou et al., 2012; Kandula et al., 2016; Lavoie Smith et al., 2015).

Three studies have reported significantly higher prevalence of peripheral neuropathy in older children during the first year of ALL treatment (Ceppi et al., 2014; Diouf et al., 2015; Lavoie Smith et al., 2015). In addition, four studies have demonstrated a correlation between race and VIPN incidence (Anghelescu et al., 2011; Diouf et al., 2015; Renbarger et al., 2008; Kishi et al., 2007). Caucasian children are at higher risk of developing VIPN than children of other origins. Two studies have investigated sex and VIPN involving children with ALL however the results were inconsistent (Diouf et al., 2015; Reinders-Messelink et al., 2000). Thus, further research is needed that evaluates how age, sex, and race affect progression of VIPN during the second year of vincristine treatment. Since this work is one of the first moderately sized studies to examine age, sex, and race, these data will strengthen the evidence on how personal characteristics influence key outcomes during year two.

A majority of patients (78%) develop neuropathy (defined as a score of 4 on a 0-28 scale) during the initial phase of treatment (Lavoie Smith et al., 2015; Toopchizadeh et al., 2009). Patterns and severity of VIPN with ALL, over the first year of treatment, are reported highest at about 6 months after treatment onset (Lavoie Smith et al., 2015). This is several months after reaching the maximum dose density of vincristine, which illustrates worsening VIPN even after the frequency of receiving vincristine has been reduced. This is known as a coasting effect.

There is limited information regarding prevalence and severity of VIPN after 12 months. Three cross-sectional studies with small sample sizes of children reported findings of chronic VIPN (six months off treatment; 30 months post diagnosis for females and 42 months post diagnosis for males) in approximately 30% to 53% of patients (Gilchrist et al., 2017; Jain et al., 2014; Kandula et al., 2018; Ramchandren et al., 2009). Roughly, 3-6% of patients develop loss of vibration sensibility and light touch abnormalities, and 30% develop chronic ankle weakness post-chemotherapy (Gilchrist et al., 2017; Jain et al., 2014). The actual incidence of loss of vibration sensibility and light touch abnormalities may be under-reported however due to a lack of gold standard measurement tool. The VIPN deficits reported are predominantly lower limb sensory axonal neuropathy (Kandula et al., 2018). VIPN severity may remain unchanged or increase as the cumulative dose of vincristine increases over 2 to 3 years of treatment (Diouf et al., 2015; Kandula et al., 2018). In addition, the second year of treatment with vincristine remains insufficiently investigated in relation to sex. Therefore, this study examined the following research questions:

RQ1: explore the impact of VIPN over time as measured monthly at 12, 15, 18, 21, and 24 months.

RQ2: explore the contribution to the impact of VIPN by evaluating the following specific nerve pathways: sensory (vibration, temperature, and extent of worst symptom), sensory/motor (reflexes), and/or motor (strength).

Methods

The Symptom Management Model (SMM; Dodd et al., 2001) was used to guide this study to test the relationship between the symptom experience and outcomes for the child experiencing peripheral neuropathy during year 2 of treatment for ALL. The SMM model has

guided studies in children with ALL experiencing other symptoms (i.e., pain, fatigue, sleep disturbance; Gedaly-Duff et al.; Van Cleve et al., 2004; Van Cleve et al., 2002) but has not been used to evaluate PN in this population. This model lends itself to the study of this population and methods used.

This secondary analysis was based on the methodology used in the parent study. The data were collected during an observational, longitudinal, prospective, multi-center study, entitled The Advance Trial NCI R01 PAR-08-248-0132428, funded by the National Cancer Institute. These analyses focused on the unexplored data from the parent study to characterize VIPN progression during the second year of ALL treatment with vincristine.

Design

The parent study used a longitudinal descriptive study. This analysis provides a descriptive and correlational examination of year 2 data from the parent study.

Sample

All data for this study were obtained from a de-identified dataset derived from pediatric patients with ALL recruited from the four comprehensive cancer centers nation-wide that participated in the trial. A brief description of the children from the parent study is provided. The study population was enrolled between 2012-2015 and consisted of pediatric patients (ages 1 - 18, mean 9.5 years) diagnosed with ALL who were scheduled to receive vincristine as part of their initial chemotherapy treatment protocol (treated according to Children's Oncology Group). For patients enrolled after receiving the first dose of vincristine, documentation of a baseline neurologic exam was required prior to the first vincristine dosage. Patients were excluded from the study if their baseline (i.e. prior to receiving any doses of vincristine) peripheral neuropathy score was greater than grade 1 (per National Cancer Institute Common Terminology Criteria

Adverse Event Scale v. 4.0), had a history of an allergic reaction to vincristine, had a history of liver disease with chronic elevation in liver function tests to greater than five times the upper limit of normal based on normal values for age (acute changes in liver function tests at the time of ALL diagnosis with no history of chronic liver disease do not require exclusion), had current active treatment with erythropoietin, were getting vitamin supplements above 100% of the recommended daily allowance, had Down's syndrome, were receiving itraconazole, had a history of co-existent serious illness or infection (infections requiring exclusion are those in which the patient has sepsis requiring admission to the Pediatric Intensive Care unit for pressors or mechanical ventilatory support, such that the baseline neurologic assessments could not be performed), or patients who were pregnant at the time of enrollment.

Using the modified Total Neuropathy Score - Pediatric Vincristine (mTNS©-PV) data collected during the second year of ALL treatment, this secondary analysis included a subset of children with mTNS©-PV between the ages of 5 - 18 (n = 86) at the start of the second year of ALL treatment for the parent study. This age group was chosen as a result of feasibility studies that indicate children were able to complete the measurement tool (Lavoie Smith, Li, et al., 2013). Nine children were removed from the dataset for attrition. Attrition was defined as participants that were missing data at 15, 18, 21, and 24 months consecutively. Two children were missing data at 21 and 24 months. Three children were missing data at 18, 21 and 24 months. Four children were missing data at 15, 18, 21, and 24 months. Participants received their first neuropathy examination prior to initiating their second dose of vincristine chemotherapy. One child in the sample relapsed during year one of ALL treatment and was moved to the very high risk protocol. None of the children died during the second year of ALL treatment.

Procedure

The TNS©-PV data were completed during the parent study each time the children received vincristine every three months during year two of therapy. Patients were followed prospectively for evaluation of vincristine-associated neuropathy throughout the course of their therapy. The TNS-PV was collected by one of three trained evaluators at each site. A pediatric neurologist and two nurse practitioner evaluators at each study site underwent training in the use of the TNS-PV. All evaluators viewed an assessment video developed by the primary investigator of the parent study. The video reviewed the TNS©-PV exam and instrument scoring details with the site neurologists who oversaw training and evaluation of nurse practitioner evaluators at the respective sites. Upon viewing the video, the site neurologist oversaw hands-on practice where nurse practitioner evaluators used instruments in a simulated setting to conduct assessments on each other. Prior to conducting TNS©-PV examinations, each evaluator practiced using the instruments with ten children with established peripheral neuropathy. These exams were conducted within the practitioner's daily work and were not supervised. Practitioners then conducted TNS©-PV exams on pediatric patients with established neuropathy. The nurse practitioner asked permission of the child and/or parent to conduct the practice exam. If either the child or parent declined, then the practice exam was not performed. After 10 practice examinations were completed, the site neurologist evaluated the neurologic examination and TNS-PV scoring proficiency using a skills competency checklist. All evaluators had to score 100% in physical examination and instrument scoring competency (evaluated by the neurologist) prior to conducting formal study assessments. If adequate skill was not demonstrated, additional practice exams were recommended by the neurologist. IRB approval was obtained for the parent study and for the secondary analysis.

Measure

Modified Total Neuropathy Score Pediatric Vincristine (mTNS©-PV)

The mTNS©-PV was used for the secondary analysis. The TNS©-PV measurement tool used by LaVoie Smith and colleagues in 2015 to analyze year one data was modified by removing two original items of constipation and hoarseness from the TNS©-PV. The removal of these two items improved the Cronbach's alpha from 0.68 to 0.84. The demographic data available was sex, race, and age. The mTNS©-PV was used to evaluate 77 children ages 5 to 18 years old who were receiving vincristine. The mTNS©-PV used in the present study is discussed in the text and table (Table 3.2) below.

The modified Total Neuropathy Score - Pediatric Vincristine (mTNS©-PV) measure quantifies subjective numbness, tingling, neuropathic pain, vibration sensibility, and temperature sensibility and it objectively measures muscle strength, and deep tendon reflexes. For the mTNS©-PV each item is scored on a 0 to 4 scale, with higher cumulative scores indicating more severe neuropathy. Internal consistency reliability was supported with a Cronbach's alpha coefficient of 0.84 (Lavoie Smith, Li, et al., 2013). The mTNS©-PV is responsive to change over time based on weekly assessment scores from baseline to week 15 (Lavoie Smith, Li, et al., 2013). PN prevalence is operationalized as a score of 4 or higher on the mTNS©-PV (range 0-20). Children with a TNS©-PV score (range 0 to 28) $\geq$ 4 were defined as having VIPN (Lavoie Smith, Li, et al., 2013). This cut point was based on finding that 5% of normal pediatric controls have a ped-mTNS (a different TNS© variant) score of four or higher, and no normal controls had scores $\geq$ 5 (Gilchrist & Tanner, 2013; Lavoie Smith, Li, et al., 2013).

The cognitive and emotional development of each child can affect their ability to report their symptoms using the mTNS©-PV (Lavoie Smith, Pang, et al., 2013). Children in this study

were asked if they had numbness, tingling, or pain and where the location of the symptom was (e.g., toes to midfoot, midfoot to ankle, ankle to knee, upper extremities). The item was scored based on the location the child indicated for any of the reported symptoms. In addition, the children were assessed for temperature sensibility by placing a cold tuning fork on their skin and asking them to report where the temperature sensibility was reduced or absent (e.g., toes to midfoot, midfoot to ankle, ankle to knee, upper extremities). Vibration sensibility was assessed with a 128 Hz weighted tuning fork placed on bony prominences beginning at distal extremities. The patient was asked to report when the vibration was no longer sensed. The nurse would then determine if the vibration sensibility was reduced or absent in certain locations (e.g., toes to midfoot, midfoot to ankle, ankle to knee, upper extremities). Self-reporting of the symptom implies perception of the presence of the symptom.

Deep tendon reflexes (i.e., ankle, patellar, triceps, brachioradialis, biceps) were assessed by the nurse using a reflex hammer. The reflexes were evaluated as ankle reflex reduced (score = 1), ankle reflex absent (score = 2), ankle reflex absent/others reduced (score = 3), or all reflexes absent (score = 4). The nurse evaluated strength through flexion/abduction exercises to parts of the child's body (i.e., toe extension/flexion, ankle dorsiflexion, hip flexion, hand grip, thumb abduction, wrist extension, arm abduction) and rated this strength as mild weakness, moderate weakness, severe weakness, or paralysis through resistance based on the weakest muscle group evaluated.

Analysis

Descriptive statistics (frequencies, means, and standard deviations) were computed. Power analysis determined that with 77 participants, there was 80% power to detect a 0.75 effect size, if the type I error was controlled at 60% (Lavoie Smith et al., 2015). The effect size is

defined as the difference between the 12-month and 24-month cumulative mTNS©-PV scores divided by the standard deviation (Lavoie Smith et al., 2015). For the 77 children, prevalence was calculated by the number of children in the sample with a mTNS©-PV score of 4 or greater during any of the months 12, 15, 18, 21, and 24 divided by the total number of children in the sample.

Approach to Missing Data

The secondary data set had missing data which can compromise inferences if missing data is not handled appropriately. Overall, there was 25% missing data points for the secondary data set. The first step in missing data analysis is to decide if the missing data is missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR). Missing completely at random is defined as the probability of missing data for a particular variable is unrelated to other measured variables (Baraldi & Enders, 2010). This means the missingness is unrelated to any variables in the study. This most likely is not the case for the secondary data set being examined. Missing at random is defined as missingness that is related to other measured variables in the analysis model (Baraldi & Enders, 2010). This is the most likely reason for the missing data because of the example given above. Children and adolescents may not be willing to participate with the nurse collecting data and age is a variable in the model. Missing not at random is defined as missing data that are systematically related to the hypothetical values which are missing. That would mean that missing data are systematically related to VIPN scores. This scenario can be common in clinical trials where children may have declining health or death. Based on secondary data set being examined, one child had a relapse during their treatment. Death was not recorded in any of the 77 children. This would not account for 25% missing data.

When data are found to be MAR, prediction of missing values can be based on the participants with complete data sets (n = 27; Jakobsen et al., 2017). Multiple imputation is considered to be superior and more powerful approach compared to other missing data techniques such as deletion or single imputation approaches because it produces unbiased estimates for both MCAR and MAR data (Baraldi & Enders, 2010). Multiple imputation, using a regression equation generated from the 27 complete data sets, was used to create five full data sets, each containing different imputed values. These data sets were then analyzed for estimates of the means and covariances to construct a set of regression equations that can predict missing data. Bayesian estimation principles were used to generate new estimates of the means and covariances which adds a random residual term to each of the resulting estimates. This process developed imputed values for the missing values.

Complete case analysis is a statistical approach based on participants with complete datasets. The complete case analysis results were then compared with the analyses that used a pair-wise approach and an imputed approach. In addition, approximately 45% of the children had one or two months of missing data. A pair-wise approach was used for children with some missing data (one or two months of missing data). The results of this analysis was compared to the complete case analysis and the imputed analysis.

Aims for the Study

For Aim 1, the change in VIPN was described over time as measured by the mean cumulative score of the mTNS©-PV (1–20; higher = more severe) monthly at 12, 15, 18, 21, and 24 months based on a retrospective sample of 77 children with ALL.

To characterize the general progression of VIPN, the average mTNS©-PV scores were computed across all subjects for months 12, 15, 18, 21, and 24. Friedman's Test, in which the

dependent variable was the average mTNS©-PV score, and the independent variable was month, was calculated to determine the maximum and minimum months, as well as determining if there are significant differences in average mTNS©-PV scores between months.

For Aim 2, the type of nerve pathway was identified (sensory, motor, and/or sensory/motor) that contributed the most to a higher VIPN score at 12, 15, 18, 21, and 24 months according to the mTNS©-PV subscales.

To characterize the temporal pattern of VIPN pathways, the average scores including all subjects were calculated for each three month time point across year two (sensory, sensory/motor, and motor). Each of the three variables (sensory, sensory/motor, and motor) will be plotted as line graphs (Y-axis) vs. time (X-axis). The combined sensory subscales will be compared to sensory/motor and motor. In addition, the three sensory subscales will be plotted separately.

Data Management

All patient data were derived from the existing dataset that was shared by the primary investigators of the parent study (The ADVANCE Trial - NCI R01 PAR-08024809132428). Only the principal investigator (PI) of this secondary analysis and the study team had access to data, which was stored in SPSS format in a double password-protected file. The dataset included de-identified raw data including demographic information, individual mTNS©-PV scores reflecting sensory and motor neuropathy, and modified total neuropathy scale scores.

Results

Sample Demographics

A total of 289 assessments were performed on 77 children during their second year of treatment. Of the 77 children, all were able to provide multiple mTNS©-PV scores over the

second year. Table 3.3 presents sample demographic characteristics based on the second year data. Using data from those providing mTNS©-PV scores (*n* =77), there were nearly equal participants of males (51%) and females (49%) and most were Caucasian (88%) and non-Hispanic (88%) children. The mean number of mTNS©-PV assessments conducted on each child was 3.8. The mean age was 8.3 years, with a range at baseline of 5 to 18 years. Attrition rate was 10.5% (n = 9).

Research Aim 1

Aim 1 explored the impact of VIPN over time as measured monthly at 12, 15, 18, 21, and 24 months. Over the second year of treatment, 56% (n = 43) of the children who provided mTNS©-PV (scores of 4 or higher out of 20 at any time point during year two) exhibited VIPN. This is less than year one prevalence rates (78%) for children with ALL measured by the TNS-PV, but the measurement tool for the year one values used a score of 4 out of a maximum 28, and is not completely equivalent. Mean total scores, standard error, and confidence intervals for each time point are presented in Tables 3.4.1-3.4.3 using three approaches to analysis of the progression. Table 3.4.1 results are based on a total of 77 children with complete imputation for missing data. Overall severity of VIPN is low with an average score of the mTNS©-PV of 3.2 across all time points. A large number of the patients had scores at or near zero which skewed the average mTNS©-PV scores to below 4. The severity during year two does not resolve by 24 months of ALL treatment.

Table 3.4.2 measures the mTNS©-PV across all participants with no missing data (n = 27). The severity remains the same compared to the analysis of 77 children with complete imputation for missing data (Table 3.4.1). The complete case analysis or analysis of participants

with no missing data also demonstrates that VIPN severity is low however, VIPN does not resolve during year two.

Table 3.4.3 measures the mTNS©-PV across all participants with some missing data. This analysis included patients with one or two missing data points over the second year. The severity remained low and was similar when compared to the complete imputation for missing data analysis and the no missing data analysis. Overall VIPN severity is low but does not return to baseline at the end of year two treatment.

Figure 3.2 illustrates the mean mTNS©-PV score over the second year of treatment for no missing data, some missing data, and complete imputation for missing data. Each of the trajectories are closely correlated to each other. The VIPN severity remains relatively constant throughout year two of ALL treatment with low severity.

Figure 3.3 demonstrates the cumulative mean mTNS©-PV based on treatment protocol each child was enrolled in. The very high risk protocol (n = 4) exhibited the highest VIPN scores for months 15, 18, 21, and 24 months however this may be the result of one child with severe VIPN that is skewing the results. One child in the very high risk protocol had severe VIPN for every time point during year two. The standard risk (n = 56), intermediate risk (n = 4), and high risk (n = 13) protocols closely follow the results represented in Figure 3.2 with VIPN remaining relatively stable during year two with low severity. The very high risk protocol and intermediate protocol have such low numbers of children enrolled in each protocol that this chart may not represent accurate VIPN progression based on protocol. The no missing data (n = 27) and some missing data (n = 58) groups were not represented in graph form because even fewer participants in these groups would not have provided reliable representation of VIPN based on protocol enrollment.

Figure 3.4.1 represents each child with VIPN with no missing data points over year two. There is one child with severe VIPN for each time point during year two and a few children who do have high scores on the mTNS©-PV at varying time points throughout year two but then improve their mTNS©-PV scores by 24 months. This graph demonstrates that there is individual variability in the progression of VIPN over year two.

Figure 3.4.2 represents each child (n = 77) with complete imputation for missing data who developed VIPN during year two. This figure demonstrates that a majority of the children have low mTNS©-PV scores during year two of ALL treatment. This figure also illustrates that a few children develop quite severe VIPN throughout year two that does not improve or resolve throughout the year.

Research Aim 2

Research aim two was to identify which type of nerve pathway (i.e., sensory, sensory/motor, motor) contributes the most to a higher VIPN score at 12, 15, 18, 21, and 24 months according to the modified TNS©-PV subscales. Figure 3.5.1 illustrates the three subscales over year two of treatment with complete imputation of missing data and the sensory/motor (reflexes) was highest throughout year two. Figure 3.5.2 illustrates no missing data cases and sensory/motor contributed the most to the mTNS©-PV score. The same result was reported using some missing data in Figure 3.5.3. The sensory and motor mTNS-PV scores were lower than the sensory/motor scores during year two in all three analyses. The sensory and motor pathways are less severe than the sensory/motor pathway over the course of year two with variable findings based on the method of analysis completed (Table 3.5).

Based on the mTNS©-PV tool, the sensory/motor item was scored as one or greater 75% (59 out of 77) of the time. The motor item was scored one or greater 39% (30 out of 77) of the

time. Sensory items (including numbness, tingling, pain, vibration sensibility, temperature sensibility) were scored one or greater 27% (21 out of 77) of the time.

Figure 3.6.1 illustrates the components of temperature sensibility, vibration sensibility, and extent of worst subjective symptom within the sensory score for children with complete imputation of missing data (n = 77). The axons for pain & temperature sensations and the axons that mediate vibration, proprioception and light touch have different diameters and different amounts of myelination, and thus may be differentially susceptible to toxins. The third subscore was determined by asking the patient to identify the worst symptom, e.g. numbness, tingling or pain, and describe which parts of the body were affected. This may reflect the severity of discomfort affecting the patient. However, the scores for these items were low and there was no differentiation even with the analysis for some missing data (Figure 3.6.3) and no missing data (Figure 3.6.2).

A nonparametric Friedman's test of differences among repeated measures was conducted for the mean mTNS©-PV score at each time point and rendered a Chi-square value of 14.44 which was significant ($p < .006$) rejecting the null hypothesis that the mean scores of the mTNS©-PV were equal at 12, 15, 18, 21 and 24 months. Post Hoc tests were completed and the Wilcoxon test evaluated the mean mTNS©-PV score for each time point and there was no significant difference between month 12 and 24 ($p = .456$). There was a statistically significant difference between 21 months and 24 months ($p < .001$). As illustrated in Table 3.4.1 and Table 3.4.2, there is a moderate amount of variability during year two.

These results describe the child’s experience of VIPN demonstrating its' moderate incidence over the second year of ALL treatment. Sensory/motor symptoms (reduced deep tendon reflexes) received the highest scores compared to other measurements during the second

year. The difference between 12 month and 24 month cumulative mean mTNS©-PV scores were not statistically significant therefore VIPN did not change in severity over year two.

Discussion

As chemotherapy regimens and survival rates of childhood ALL patients continue to improve, common but poorly understood toxicities of therapy have emerged as an important area of focus. The principal toxicity for children with ALL is VIPN which can result in impaired gait and balance, muscle weakness, and decreased physical function (Gilchrist & Tanner, 2016; Gocha Marchese et al., 2003; Tay et al., 2017) all of which negatively impact quality of life into survivorship.

Using the sensitive modified TNS©-PV assessment tool, this study was able to reveal that 56% of children exhibited VIPN during the second year of treatment for ALL based on a score of 4 or higher on the mTNS©-PV (range 0-20). The prevalence rate during year two of treatment decreased compared to the first year of treatment (78%) based on a score of 4 or higher on the TNS-PV (range 0-28; Lavoie Smith et al., 2015). The score of 4 as a cut point for VIPN may have been too high for the mTNS©-PV which would decrease the percentage of patients experiencing VIPN. An equivalent number for the mTNS©-PV may be closer to 2.8. If 2.8 were used as the cut point for prevalence for VIPN during year two, 71% (n = 55) of ALL children exhibited VIPN. The decreased prevalence also correlates with previous findings that treatment-related risk factors, including cumulative dosing and greater drug concentrations, does not lead to worsening of VIPN during treatment (Crom et al., 1994; Kandula et al., 2016; Lavoie Smith et al., 2015; Okada et al., 2014; Smitherman et al., 2017; Teusink et al., 2012; Van Schie et al.., 2011; Verstappen et al., 2005).

The mean TNS©-PV score (range 0-28) during the first year of treatment for ALL was 4.08 (SD = 3.56) or 14.6% using the TNS©-PV (Lavoie Smith et al., 2015). The mean mTNS©-PV (range 0-20) during year two of treatment for ALL was 3.20 (SD = 2.8) or 16% indicating that VIPN remained similar in severity over the two year period. During the second year of treatment, the severity remained relatively stable across all five time points yet VIPN did not resolve by 24 months (Table 3.4, Figure 3.2, Figure 3.3). The sample had a large amount of scores at or near zero which did pull the overall mean mTNS©-PV scores down.

The mean cumulative mTNS©-PV score stratified by treatment protocols may be indeterminate (Figure 3.3). There was significantly higher number of children enrolled in the standard protocol (n = 56) compared to the other three protocols. Very few children were enrolled in the very high (n = 4), intermediate (n = 4), and high (n = 13) risk protocols. In addition, very high risk and high risk protocols have older children enrolled compared to the standard risk protocol. Studies have identified older age as a risk factor for more severe VIPN. Age may have an interaction effect in this exploratory finding. In addition, based on dose density for the child, the very high risk protocol would seem to have the most severe VIPN scores yet the high risk protocol patients had more severe VIPN. This also supports previous literature indicating that the cumulative dose of vincristine does not affect VIPN during treatment. The high risk protocol group had one child with very severe VIPN that most likely skewed these findings.

The analysis with no missing data cases (n = 27) and the completely imputed cases (n = 77) had one child with severe VIPN (> 15 on the mTNS©-PV). This child was kept in the analysis even though they would be considered an outlier because they were measured at every time point using the mTNS©-PV and this depicts one child's experience. This participant is

female, Caucasian, age 14, and on a high risk protocol. This child had no dose reductions or changes in her vincristine dosing during one or year two of treatment for ALL. The severity of her VIPN could be the result of a genetic polymorphism causing more severe VIPN or she is concurrently taking a medication that causes slowed liver metabolism of vincristine resulting in more severe VIPN (Li et al., 2019). In contrast, a majority of the children had low severity of VIPN throughout year two.

Figure 3.2 illustrates the three different methods of analysis for the cumulative mTNS©-PV scores which are 1) no missing data cases, 2) some missing data (one or two months of data missing, and 3) imputed data. By overlaying these three methods of analysis, the general trend of the data is highly correlated in all three types of analyses. The VIPN severity is low and consistent across year two of ALL treatment but does not resolve during year two treatment. In fact this correlates with recent studies investigating children 6 months to 8 years after ALL treatment that report a 30% to 50% prevalence of VIPN (Kandula, et al., 2016; Kandula et al., 2018).

In addition to investigating the cumulative mTNS©-PV scores, the sensory, sensory/motor, and motor pathways were investigated. Subscales of the mTNS©-PV were analyzed indicating that the sensory/motor subscale (i.e., deep tendon reflexes) elicited the highest scores over the second year of ALL treatment. Interestingly, sensory/motor changes have been shown to be common amongst long term ALL survivors as well (Kandula et al., 2016). Another more recent study identified the sensory pathway as the most prevalent in ALL survivors (Kandula, et al., 2018). For the sensory/motor pathway, deep tendon reflexes are tested which produces an involuntary reaction in a muscle after passive stretch by percussion of the tendon. Although the reflex has a sensory and motor component, electrophysiological testing

(Toopchizadeh et al., 2009) indicated that the motor pathway is most severely affected in VIPN. Since sensory/motor neuropathy is reported during year one and year two of ALL treatment, interventions focused on this pathway should be implemented early in ALL treatment.

The second most affected subscale was the vibration sensibility. Vibration sensibility had the highest score of the sensory items during year one as well (Lavoie Smith et al., 2015). The sensory pathway in general was reported to not resolve during survivorship 6 months after treatment has stopped (Kandula et al., 2018). The result of this study indicates that sensory neuropathy remains throughout treatment for ALL. Safety interventions for children with sensory neuropathy who cannot feel their hands or feet should be a priority during ALL treatment.

Finally, the motor subscale remained stable during the second year. Again with vincristine dosing being less frequent during year 2, and the child becoming more active during year 2 of treatment for ALL, there may be an opportunity for restoration of some axon function or accommodation that would result in improvement over time. However, one study of 531 adult survivors of pediatric cancers revealed evidence that exposure to cumulative doses of vinca-alkaloids significantly increases the risk of motor, but not sensory, impairment in adulthood (Ness, et al., 2013). Thus patients on ALL treatment for longer periods of time, including boys who undergo treatment for an additional year beyond females, may in fact have worse motor neuropathy compared to girls. Investigating the differences between boys and girls with neuropathy would be an important next step.

During the first year of ALL treatment, mean sensory/motor scores were significantly higher than sensory scores and motor scores (Lavoie Smith et al., 2015). This is also the case for year two of ALL treatment and into survivorship (Kandula et al., 2016). In order to produce deep tendon reflexes, afferent sensory neurons from muscle spindles stimulated by tapping the tendon

enter the spinal cord through the dorsal root, and directly synapse with motor neurons in the ventral horn. Efferent motor neurons travel to the appropriate muscle fibers to cause contraction to produce the reflex. A decrease in deep tendon reflexes can be caused either by deficits in the sensory component, deficits in the motor component, or both. Therefore, interventions should target both the sensory and motor pathways. In addition, safety should be an important consideration for children who cannot feel their hands or feet, cannot feel pain, or hot and cold temperatures.

The description and exploratory analysis of VIPN trajectory in children during year two of ALL add to the science due to the rigorous depth of the uninvestigated trends past year one on the impact of VIPN. This study included a moderate but acceptable sample size (280 assessments in 77 children) from a parent study with a longitudinal study design with use of the modified TNS©-PV that enabled for a more accurate VIPN description and trajectory than previously published reports using smaller sample sizes and cross-sectional designs. Although this is the first study investigating the trajectory of VIPN over the second year of treatment for ALL, these factors most likely explain a higher incidence rate than previously reported during the first year of treatment for ALL. These findings could be greatly enriched by the availability of clinical and treatment data such lab findings, co-morbidities, detailed protocol regimens beyond vincristine dosing, any supplements taken during treatment, and physical function scores.

Interventions should be tested on children during year one as VIPN begins to worsen and prior to the second year of ALL treatment. Interventions to reduce VIPN should continue throughout year two of ALL treatment. Examining experimental methods to mitigate sensory and motor peripheral neuropathy would be the next steps for research. Long term, children who develop VIPN may benefit from axon regeneration and therefore recover following the

neurotoxic exposure to the nerve. Peripheral nerves have a strong potential for axonal regeneration in the setting of toxic neuropathy (Jortner, 2020). Murine models and human studies have demonstrated that the peripheral nervous system has a robust potential for regrowing fibers that have been damaged as the result of a neurotoxic medication (Jortner, 2020). The degree of injury affects the ability of the nerve to regenerate. This process of regeneration may occur as neurotoxicity exposure becomes less frequent during year 2 of ALL treatment and after exposure has ended.

This study adds to the growing body of evidence showing a high incidence of VIPN in children, specifically sensory/motor neuropathy that does not resolve during the second year of ALL treatment. This study characterizes the variability in presentation and trajectory of VIPN in the second year of ALL treatment.

Limitations

This study has limitations. The data was not collected prospectively, thus analysis was limited to the variables collected in the parent study. Multiple imputation was used to impute missing data. A small portion of the data were collected as parent-by-proxy since some of the children may not have understood the questions being asked or were not able to answer for other reasons. The sample size was moderate. A larger sample size would elucidate more detail of this phenotype of children with ALL. Thus, studies in larger samples are needed to validate the study findings. The sample size was predominantly Caucasian thus making the generalizability of the results limited. Children age 5 to 18 were analyzed by age. In future studies, stratifying children based on by developmental stage or by school year (i.e., elementary, middles school, high school) may indicate statistical significance for future studies. Additional data on functional status and quality of life would have provided the ability to examine more distal outcomes.

Lastly, these data are limited by inadequate clinical and treatment data due to the nature of available data for this secondary analysis.

Conclusion

Research Implications

The study informs researchers regarding the continuation of peripheral neuropathy into the second year, but overall severity is no different than at 12 months. Due to the continuation of peripheral neuropathy during year two of ALL treatment, treatment and symptom management interventions for VIPN should be implemented during the first year of ALL treatment and continue throughout year two. This study provided specificity as to which nerve pathway should be targeted (sensory/motor). Knowledge regarding the temporal patterns of progression or recovery of a specific type of nerve dysfunction (e.g., sensory/motor neuropathy) can be used to design targeted interventions that can be introduced at well-informed time points to affected children. Oncology nurse scientists have expertise in the development and testing of symptom-focused interventions and are well poised to address the management gaps with VIPN in children.

Nursing Practice Implications

VIPN is a common toxicity in children undergoing treatment for ALL who are likely to be cured of their disease but may experience serious long-term VIPN-associated consequences of health, function, and quality of life. In addition, the development of neuropathy has been shown to interfere with childhood development and lead to physical inactivity with consequences of long-term health problems such as obesity and diabetes (Mody et al., 2008; Silverman, 2014). This study informs nurses as to when detailed assessments, ongoing monitoring, and interventions should be considered for VIPN in children.

Innovation

This study adds to nursing knowledge by addressing the paucity of published papers on the second year of treatment for children experiencing VIPN. Further, the mTNS©-PV measures provides highly specific neuropathy phenotype data that has not been obtained and utilized previously for year two in a pediatric ALL population. In addition, describing the incidence, severity, and temporal patterns of sensory, sensory/motor, and motor neuropathy can inform oncology nurse scientists about what type of intervention to develop and test for children with VIPN. The study also provides detailed information on the timing to implement and test targeted interventions.

APPENDIX

Figure 3.1

Stocking and Glove Distribution of Peripheral Neuropathy in Children

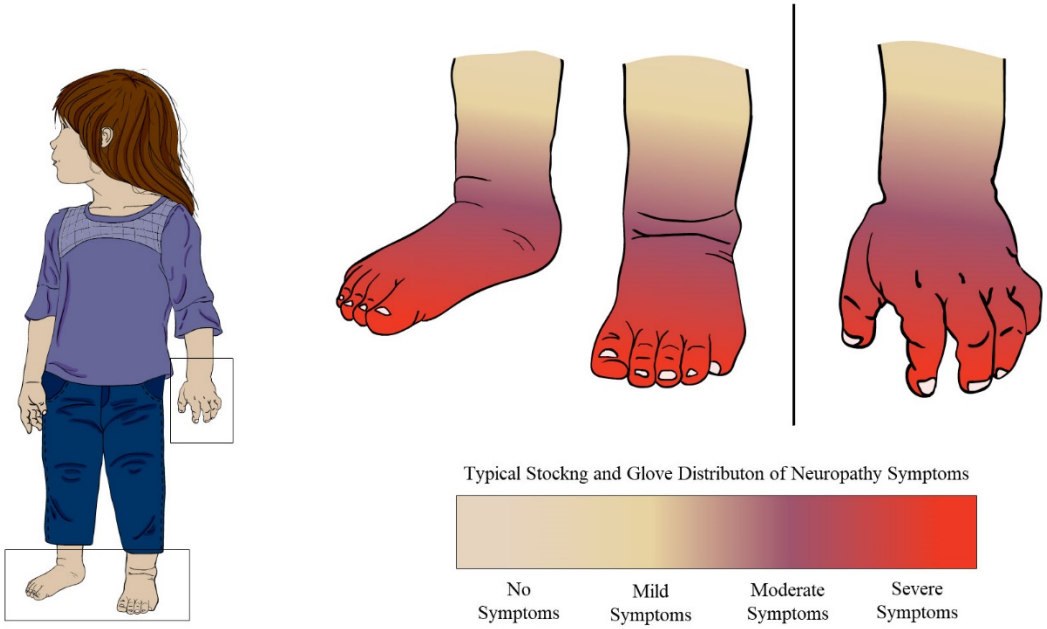


Table 3.1

Children's Oncology Group Treatment Protocol Eligibility[a]

Protocol	Age at diagnosis	Initial WBC	Other qualifiers	Vincristine dosing
Standard Risk B-cell ALL (AALL0932)	1 – 9.99	> 50,000/uL	No central nervous system involvement (i.e., presence of leukemic blasts in CNS fluid that contains at least 5 white blood cells per microliter), no testicular involvement, no Down's syndrome	1.5 mg/m2 (2 mg maximum
Standard Risk B-cell ALL (AALL0331)	1 – 9.99	> 50,000/uL	Central nervous system involvement is classified. No testicular leukemia eligible.	1.5 mg/m2 (2 mg maximum)
High risk B-cell ALL (AALL0232)	1-9 years of age with WBC > 50,000; 10-30 age with any WBC	Variable		1.5 mg/m2 (2 mg maximum)
Very high risk B-cell ALL (AALL1131)	Eligible age 1-9.99 with WBC > 50,000, testicular leukemia, or CNS 3. Eligible age > 10 with any WBC, testicular leukemia, or CNS 3.	Variable		1.5 mg/m2 (2 mg maximum)

[a] Borowitz et al., 2015; Maloney et al., 2020; Salzer et al., 2015; Salzer et al., 2018

Table 3.2

Modified Total Neuropathy Score©-Pediatric Vincristine (mTNS©-PV; Cornblath et al., 1999; Lavoie Smith, Li, et al., 2013)

Symptom	0	1	2	3	4
Worst subjective symptom (tingling, numbness, or pain)	None	Toes to midfoot, excluding heel	Midfoot to ankle	Extend above ankle to knee; no upper extremity involvement	Above the knee and upper extremity symptoms
Temperature sensibility	Normal	Absent/reduced from toes to midfoot	Absent/reduced from midfoot to ankle	Absent/reduced above ankle to knee	Absent/reduced above the knee or in lower and upper extremities
Vibration sensibility	Normal	Absent/reduced from toes to midfoot	Absent/reduced from midfoot to ankle	Absent/reduced above ankle to knee	Absent/reduced above the knee or in lower and upper extremities
Strength	Normal	Mild weakness, able to overcome resistance	Moderate weakness, can overcome gravity but not resistance	Severe weakness, cannot overcome gravity	Paralysis
Tendon reflexes	Normal	Ankle reflex decreased	Ankle reflex absent	Ankle reflex absent, others decreased	All reflexes absent

Table 3.3

Sample Demographics

Variable	*n* (*N* = *77*)	%	*M*	*SD*
Age			8.3	3.82
Sex (*N* = *77*)				
Female	38	49		
Male	39	51		
Race				
White	68	88		
Non White	9	12		

Table 3.4.1

Mean Cumulative Vincristine-Induced Peripheral Neuropathy Scores at Months 12, 15, 18, 21, 24 (N=77) With Complete Imputation for Missing Data

Month	Mean cumulative mTNS©-PV Score (*M*)	SE	95% CI
12	3.4	0.3	2.7, 4.0
15	3.0	0.4	2.3, 3.7
18	3.1	0.4	2.3, 4.0
21	2.8	0.3	2.1, 3.5
24	3.7	0.4	2.9, 4.6

Note. mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

Table 3.4.2

Mean Cumulative Vincristine-Induced Peripheral Neuropathy Scores at Months 12, 15, 18, 21, and 24 (N=27) With No Missing Data

Month	Mean cumulative mTNS©-PV Score (*M*)	SE	95% CI
12	3.1	0.7	1.6, 4.7
15	2.9	0.8	1.2, 4.6
18	2.6	0.9	0.8, 4.3
21	2.1	0.8	0.6, 3.7
24	2.9	0.9	1.1, 4.7

Note. mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

Table 3.4.3

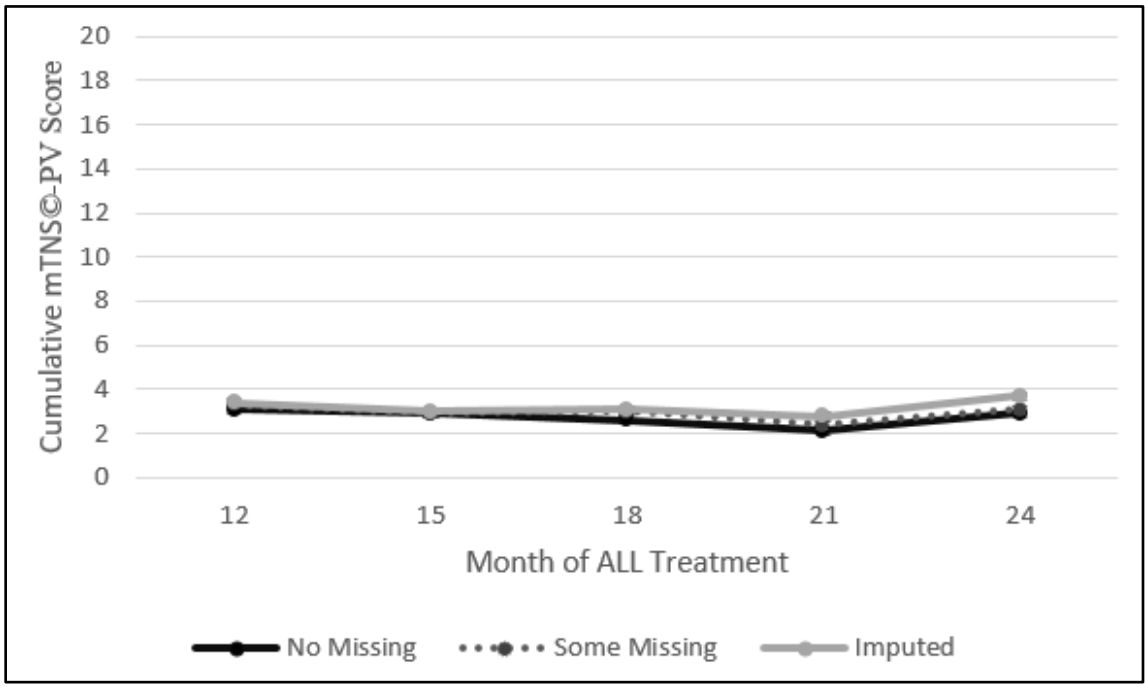
Mean Cumulative Vincristine-Induced Peripheral Neuropathy Scores at Months 12, 15, 18, 21, 24 With Some Missing Data

Month	Mean cumulative mTNS©-PV Score (*M*)	SE	95% CI
12	3.3 (n=62)	0.7	2.2, 3.7
15	2.9 (n=66)	0.8	2.2, 3.6
18	3.0 (n=65)	0.7	2.0, 3.6
21	2.4 (n=51)	0.8	0.8,4.1
24	3.1 (n=45)	0.9	1.6, 4.7

Note. mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

Figure 3.2

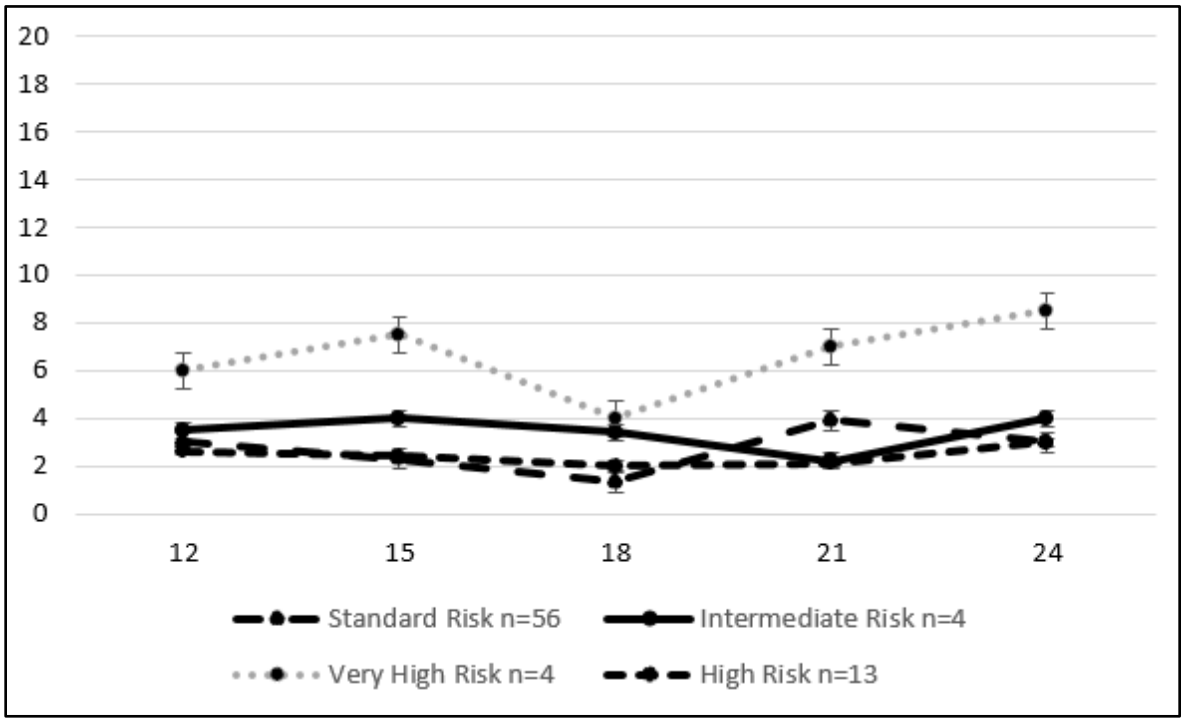
Mean Cumulative mTNS©-PV Score by Month for No Missing Data Analysis (N=27), Some Missing Data Analysis (N=58), and With Complete Imputation of Missing Analysis (N=77)



Note. mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

Figure 3.3

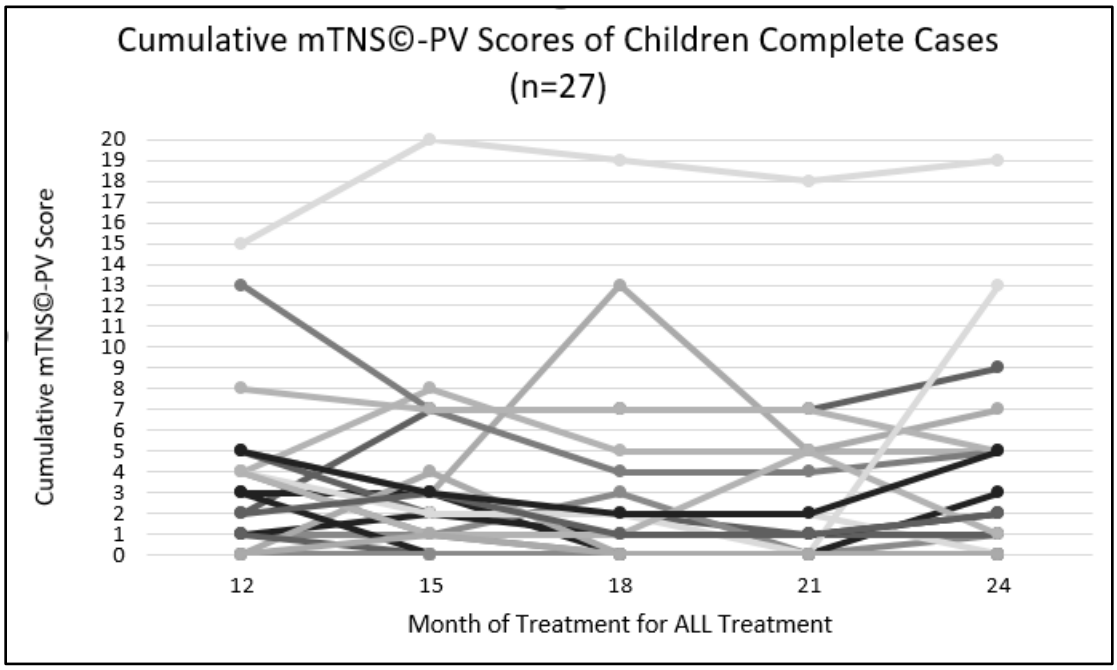
Mean Cumulative mTNS©-PV Score Stratified by Risk Protocol With Complete Imputation of Missing Data (N=77)



Note. mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

Figure 3.4.1

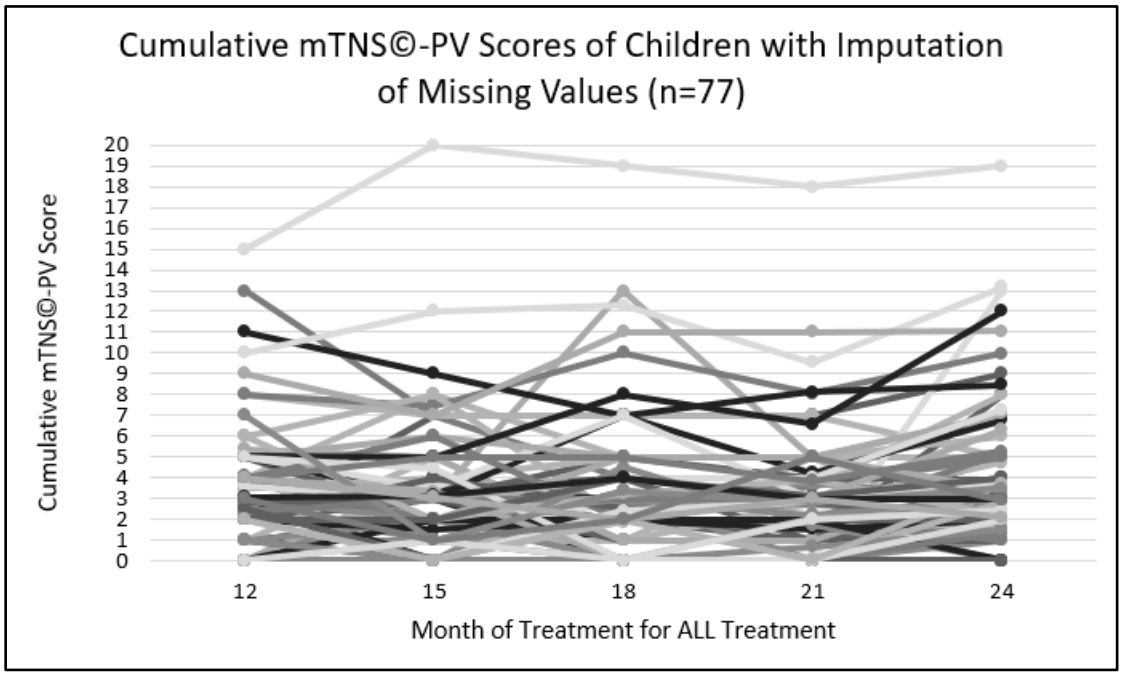
Individual Cumulative mTNS©-PV Scores of Children with No Missing Data (N=27)



Note. mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

Figure 3.4.2

Individual Cumulative mTNS©-PV Scores of Children With Complete Imputation for Missing Data (N=77)



mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

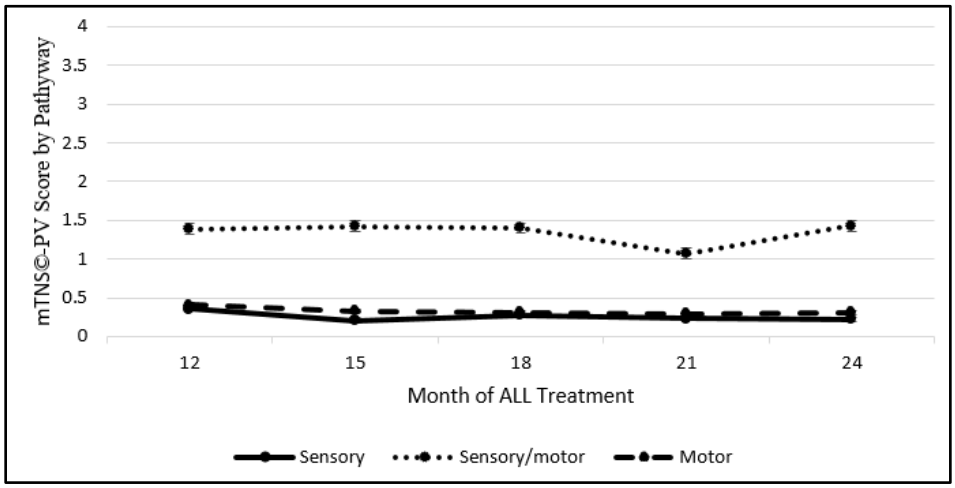
Table 3.5

Subscales of the mTNS©-PV by Month for No Missing Data Analysis (N=27), Some Missing Data Analysis (N=58), and with Complete Imputation of Missing Analysis (N=77)

Time Point	Analysis Approach	Sensory/Motor	Sensory	Motor
12 Months	No Missing Data	0.93	0.59	0.52
	Some Missing Data	1.38	0.40	0.42
	Completely Imputed Data	1.39	0.36	0.41
15 Months	No Missing Data	1.19	0.37	0.41
	Some Missing Data	1.40	0.43	0.48
	Completely Imputed Data	1.42	0.21	0.33
18 Months	No Missing Data	1.00	0.44	0.26
	Some Missing Data	1.39	0.40	0.30
	Completely Imputed Data	1.40	0.28	0.31
21 Months	No Missing Data	0.85	0.33	0.26
	Some Missing Data	1.05	0.30	0.29
	Completely Imputed Data	1.07	0.23	0.29
24 Months	No Missing Data	1.04	0.41	0.22
	Some Missing Data	1.41	0.35	0.30
	Completely Imputed Data	1.43	0.22	0.31

Figure 3.5.1

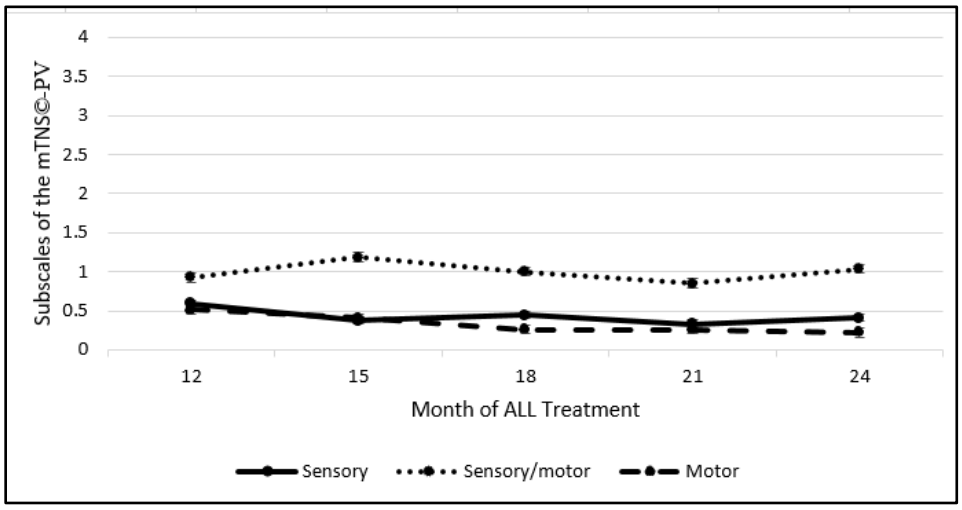
Subscales of the mTNS©-PV by Month With Complete Imputation of Missing Data (N=77)



Note. mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

Figure 3.5.2

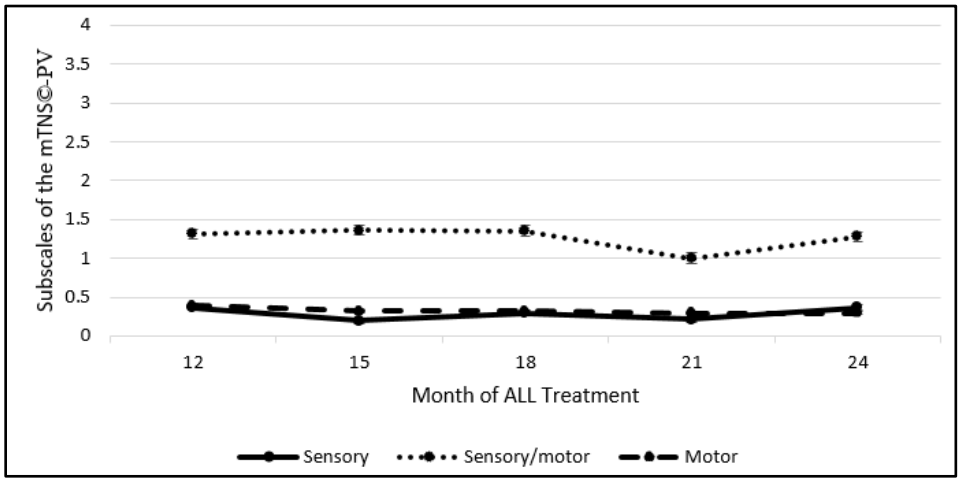
Subscales of the mTNS©-PV by Month With No Missing Data Analysis (N=27)



Note. mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

Figure 3.5.3

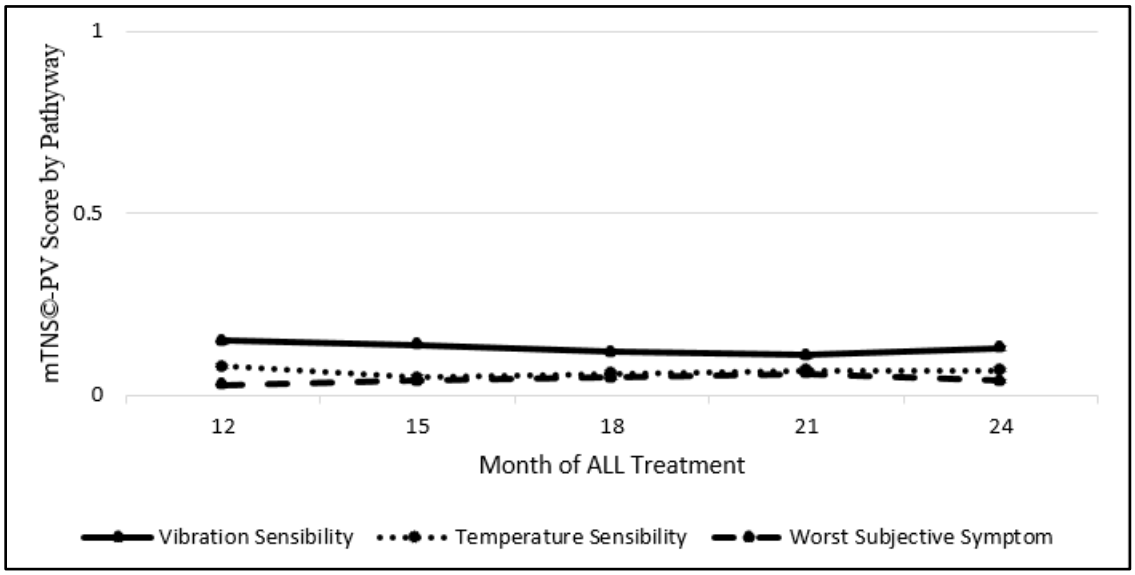
Subscales of the mTNS©-PV by Month With Some Missing Data Analysis (N=58)



Note. mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

Figure 3.6.1

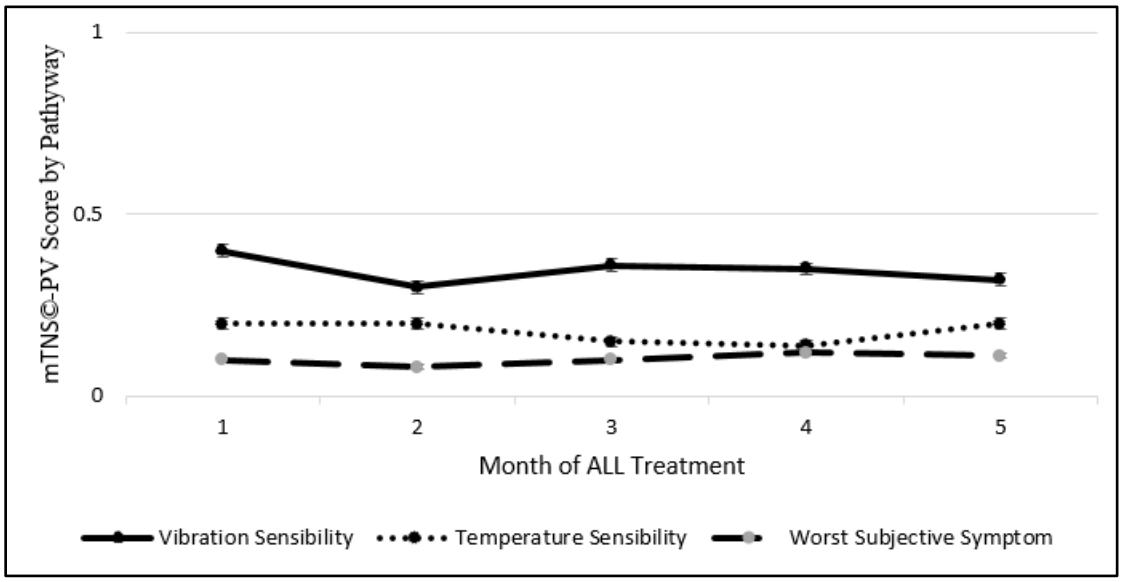
Subscales of the Sensory Component by Month With Complete Imputation of Missing Data (N=77)



Note. mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

Figure 3.6.2

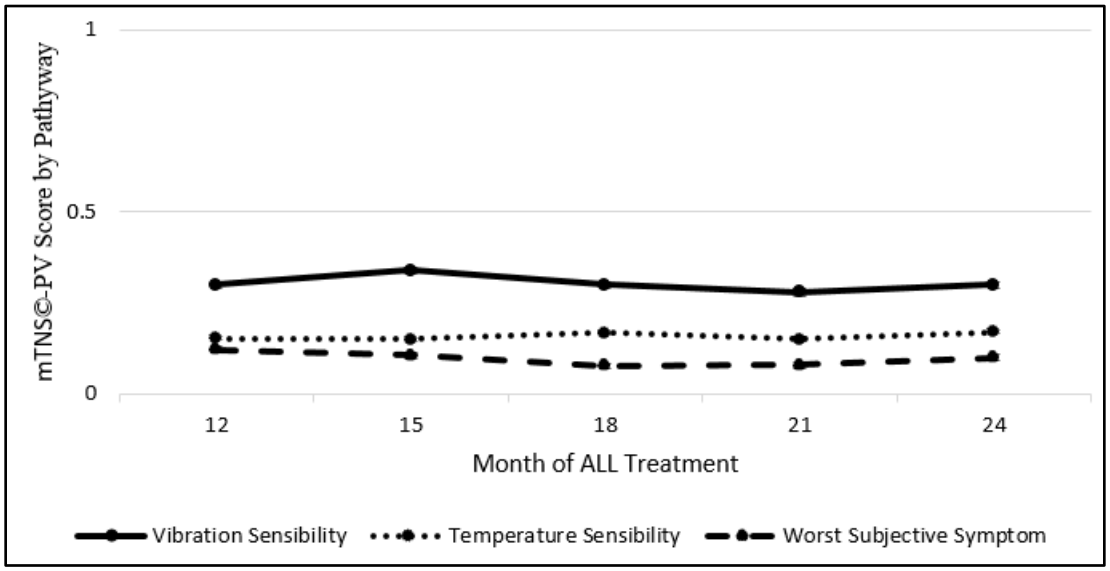
Subscales of the Sensory Component by Month With No Missing Data Analysis (N=27)



Note. mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

Figure 3.6.3

Subscales of the Sensory Component by Month With Some Missing Data Analysis (N=58)



Note. mTNS©-PV, modified Total Neuropathy Score-Pediatric Vincristine

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CHAPTER 4: PATIENT CHARACTERISTICS PREDICTIVE OF PERIPHERAL NEUROPATHY IN CHILDHOOD CANCER PATIENTS DURING YEAR TWO OF TREATMENT

Abstract

A majority of children who receive vincristine for the treatment of acute lymphocytic leukemia (ALL) develop vincristine-induced peripheral neuropathy (VIPN) during the first year of treatment. VIPN can negatively affect physical function and may require the reduction or withdrawal of chemotherapy. Severe symptoms including painful numbness and tingling in the hands and feet manifest as impaired gait, balance, and impaired physical function, thus negatively impacting health-related quality of life during ALL treatment. Progressive increased risk of vincristine neurotoxicity has been observed in children based on older age, genetic mutations, dose, and concurrent medications. Contradictory findings have been observed for cumulative dose and stage of ALL as risk factors.

The retrospective study, guided by the adapted Symptom Management Model, examined patient characteristics (i.e., age, sex, race) and treatment characteristics (i.e., VIPN at 12 months) that may be associated with more severe VIPN during the second year of treatment. During year one, older age and Caucasian race has been shown to be risk factors for VIPN. Describing these yet-to-be-examined patient characteristics during year two of ALL treatment would allow for resource appropriation to patients at higher risk, as well as potentially permitting dose escalation in patients with low toxicity to improve survival. In addition, this will guide researchers in developing future targeted interventions to be tested on children at high risk for severe VIPN. Currently, there are no guidelines for the assessment of VIPN in children or evidence-based treatment strategies for VIPN.

Utilizing secondary data, this study examined 77 children with ALL to determine whether demographic variables (i.e., race, sex, and age) or treatment variables (VIPN total score at 12 months) were associated with VIPN at 24 months. The modified Total Neuropathy Score - Pediatric Vincristine (mTNS©-PV) at five time points during year two of ALL treatment was used to measure peripheral neuropathy and ordinary least square regression models were fitted.

For children who were exposed to vincristine during year two, the interaction of the mTNS©-PV female sex scores at 12 months were significantly positively associated with mTNS©-PV scores at 24 months (coefficient 0.5620, $p < 0.04$). Age, sex, race, and VIPN at 12 months were not independently found to be significantly associated with mTNS©-PV scores at 24 months.

Age, sex, race, and VIPN at 12 months were not significant predictors of peripheral neuropathy at 24 months independently. This study adds to the science regarding potential predictors for VIPN during year 2 of treatment. Identifying risk factors for VPIN can support and guide resource allocation and clinical guidelines for year two of ALL treatment. Children with low risk of worsening VIPN could be considered for dose escalation during year two of treatment for ALL to increase survival. Children with high risk of worsening VIPN should have increased surveillance and early intervention.

Introduction

For children undergoing treatment for Acute Lymphocytic Leukemia (ALL), vincristine is an antineoplastic agent that is the cornerstone of multimodal treatment. Vincristine is commonly used due to its high response rates, low rates of myelosupression, and increased tolerance by children to relatively higher doses (Nama et al., 2020). However, children receiving vincristine commonly develop drug toxicities including vincristine-induced peripheral

neuropathy (VIPN), which is a serious and pervasive problem, resulting in progressive, distal to proximal length-dependent nerve damage. Often the development of VIPN can result in drug dosage reductions that decrease therapeutic efficacy (Nama et al., 2020).

Fortunately, survival for pediatric patients with ALL has improved dramatically over the past several decades as a result of clinical trials and the use of vincristine. Currently, long-term survival rates are nearly 90%, compared to 50 years ago when the survival rate of pediatric ALL was 10% to 20% (Tai et al., 2017). However, treatment-related toxicities including vincristine-induced peripheral neuropathy (VIPN) are very common and affect the majority of children being treated for ALL (Kandula et al., 2016). Peripheral neuropathy is the development of distal to proximal sensory and motor nerve damage that can result from a variety of neurotoxic chemotherapy agents. Vincristine has a broadly reproducible pattern affecting the sensory, sensory/motor, and motor pathways of the peripheral nervous system. Children describe numbness, tingling, and neuropathic pain in the fingers and toes. Motor impairment manifests as foot drop, gait abnormalities, and muscle weakness (Lavoie Smith et al., 2015). As a result of VIPN, children have functional impairment and decreased quality of life (Fardell et al., 2017). Several key characteristics have been investigated with VIPN during the first year of treatment for ALL (Kandula et al., 2016). These key characteristics such as age, sex, and race warrant examination during year two since children receive treatment for at least 2 years and in some cases longer. Describing these patient characteristics would allow for resource allocation to patients at higher risk, as well as potentially permitting dose escalation in patients with low toxicity to improve survival.

Patient Characteristics of VIPN

Research has investigated some correlations of VIPN during the first year of treatment for ALL. The relationship between VIPN and age has been contradictory. A significantly higher prevalence of VIPN has been reported in younger children during year one of treatment (Vainionpaa et al., 1995). Vainionpaa and colleagues (1995) evaluated VIPN using neurological exams completed by a neurologist. Ten percent (4 out of 40) of children (average age of 21.5 months) developed severe VIPN and were unable to walk or support themselves due to muscle weakness and nerve damage. However, three more recent studies have reported significantly higher prevalence in older children during the first year of ALL treatment (Diouf et al., 2015; Lavoie Smith et al., 2015; Ceppi et. al., 2014). One study that reported a higher prevalence in older children assessed VIPN drawing upon retrospective chart reviews using an adverse event scale instead of a valid and reliable measurement tool (Ceppi et al., 2014). Seven studies have not found any association between age and VIPN in children (Anghelescu et al., 2011; Crom et al., 1994; Gutierrez-Camino et al., 2016; Toopchizadeh et al., 2009; Yildiz & Temucin, 2016). Due to such inconsistent findings during year one, it is difficult to build on these results when examining year two; nonetheless, year two investigations should include the demographic of age.

Again, building upon the state of the science for year one symptoms, other demographics were examined. Thirteen studies reported race and/or ethnicity of the children involved in ALL research (Anghelescu et al., 2011; Aplenc et al., 2003; Crom et al., 1994; Diouf et al., 2015; Egbelakin et al., 2011; Kishi et al., 2007; Lavoie Smith et al., 2013; Lavoie Smith et al., 2015; Plasschaert et al., 2004; Renbarger et al., 2008); however only five of the studies investigated the relationship between VIPN and race (Anghelescu et al., 2011; Diouf et al., 2015; Kishi et al., 2007; Renbarger et al., 2008). A significant relationship between race and VIPN was

demonstrated in four studies (Anghelescu et al., 2011; Diouf et al., 2015; Kishi et al., 2007; Renbarger et al., 2008), reporting that Caucasian children were at higher risk of developing VIPN than children of other racial and ethnic background. Caucasian children are more likely to not have CYP3A5 allele which produces CYP3A5 enzyme (Egbelakin et al., 2011; Renbarger et al., 2008). This enzyme metabolizes vincristine efficiently. Caucasian children do not metabolize vincristine proficiently thus they develop more severe VIPN. This is most likely why African American children do not develop VIPN yet have higher mortality rates for ALL (Renbarger et al., 2008). One study did not demonstrate a significant relationship between race and VIPN during year one of treatment for ALL however there was a significantly higher percentage of Caucasian children (88%) in the study (Lavoie Smith et al., 2015). Due to the contradictory findings and the lack of use of valid and reliable tools used, race should be investigated during year two.

One of the most inconsistent findings during year one was the differences found between boys and girls. Current ALL treatment consists of multimodal chemotherapy regimens divided into treatment phases which typically last two years for girls and three years for boys (National Comprehensive Cancer Network, 2016). Boys are more likely to relapse after treatment for ALL thus their regimen lasts longer. Sex and VIPN was investigated in two studies involving children with ALL (Diouf et al., 2015; Reinders-Messelink et al., 2000). One study found a significant relationship between sex and VIPN indicating that girls develop more VIPN compared to boys during year one of ALL treatment (Diouf et al., 2015). The other study found that boys are at higher risk for developing VIPN during the first year of ALL treatment (Reinders-Messelink et al., 2000). Moreover, six studies did not find a significant relationship between sex and VIPN in children (Anghelescu et al., 2011; Lavoie Smith et al., 2015; Gutierrez-Camino et al., 2016;

Kishi et al., 2007; Renbarger et al., 2008; Yildiz & Temucin, 2016). Therefore, sex is a critical variable to retain in any study of year two VIPN.

Standard Care for VIPN Symptoms

Treatment-related risk factors, including cumulative dose and greater drug concentrations, are not well established in pediatric patients (Crom et al., 1994; Okada et al., 2014; Smitherman et al., 2017; Teusink et al., 2012; Van Schie et al., 2011; Verstappen et al., 2005). However, despite the lack of direct evidence associating drug concentration and VIPN in children, treatment protocols recommend vincristine dose reduction if VIPN becomes severe (Gaynon et al., 2010). Better assessment is needed with a valid and reliable measure of patient reported outcomes such as the modified Total Neuropathy Score - Pediatric Vincrstine (mTNS©-PV) to understand the association between patient factors and VIPN severity over year two of treatment. If there are significant associations, nurses and other providers can allocate appropriate resources for individuals at higher risk for VIPN during year two.

Therefore, this study examined the following research question:

RQ1: explore the demographic characteristics (i.e., race, sex, age) and treatment characteristics (VIPN at 12 months) of children with ALL suffering from VIPN at 12 months as predictor variables for VIPN at 24 months based on the cumulative score of the mTNS©-PV.

Methods

Guided by the current evidence and the Symptom Management Model (Dodd et al., 2001), the purpose of this study was to determine if patient demographics and treatment characteristics of children being treated for ALL are associated with severe VIPN during the second year of treatment. This model lends itself to the study of this population and methods use.

This secondary analysis was based on the methodology used in the parent study. These data were collected during an observational, longitudinal, prospective, multi-center study, entitled The Advance Trial R01 PAR-08-248-0132428, funded by the National Cancer Institute. These analyses focused on the unexplored data from the parent study to examine demographic characteristics (i.e., race, sex, age) and treatment characteristics (VIPN at 12 months) of children with ALL suffering from VIPN as predictor variables for VIPN at 24 months.

Design

The parent study used a longitudinal descriptive study. This analysis provides a descriptive statistics (mean and standard deviation) for the sample population. Ordinary least squares regression models were used to test the hypothesis that demographic and treatment characteristics at 12 months were predictors of VIPN at 24 months. Relevant variables (i.e., age, race, sex, and VIPN total score at 12 months) were analyzed to determine how VIPN scores change over time considering these specific patient and treatment characteristics and the amount of imputed data.

Sample

All data for this study were obtained from a de-identified dataset derived from pediatric patients with ALL (n = 77) recruited from the four comprehensive cancer centers nation-wide that participated in the trial. A brief description of the children from the parent study is provided. The study population were enrolled from 2012 to 2015 and consisted of pediatric patients (ages 1 - 18, mean 9.5 years) diagnosed with ALL who were scheduled to receive vincristine as part of their initial chemotherapy treatment protocol (treated according to Children's Oncology Group). For patients enrolled after receiving the first dose of vincristine, documentation of a baseline neurologic exam was required prior to the first vincristine dosage. Patients were excluded from

the study if their baseline (i.e. prior to receiving any doses of vincristine) peripheral neuropathy score was greater than grade 1 (per NCI CTC v. 4.0), had a history of an allergic reaction to vincristine, had a history of liver disease with chronic elevation in liver function tests to greater than five times the upper limit of normal based on normal values for age (acute changes in liver function tests at the time of ALL diagnosis with no history of chronic liver disease do not require exclusion), had current active treatment with erythropoietin, was getting vitamin supplements above 100% of the recommended daily allowance, had Down's syndrome, were receiving itraconazole, had a history of co-existent serious illness or infection (infections requiring exclusion are those in which the patient has sepsis requiring admission to the Pediatric Intensive Care unit for pressors or mechanical ventilatory support, such that the baseline neurologic assessments may not be performed), or patients who were pregnant at the time of enrollment.

Using the modified Total Neuropathy Score - Pediatric Vincristine (mTNS©-PV) data collected during the second year of ALL treatment, this secondary analysis included a subset of children with mTNS©-PV between the ages of 5 - 18 (n = 77) at the start of the second year of ALL treatment for the parent study. This age group was chosen as a result of feasibility studies that indicate children were able to complete the measurement tool (Lavoie Smith et al., 2013). Nine children were removed from the dataset for attrition. Attrition was defined as participants that were missing data at 15, 18, 21, and 24 months consecutively. Two children were missing data at 21 and 24 months. Three children were missing data at 18, 21, and 24 months. Four children were missing data at 15, 18, 21, and 24 months. Participants received their first neuropathy examination prior to initiating their second dose of vincristine chemotherapy. One child in the sample relapsed during year one of ALL treatment and was moved to the very high

risk protocol. None of the children died during the second year of ALL treatment. All children included in the secondary analysis were undergoing ALL treatment and receiving vincristine.

Procedure

The mTNS©-PV data were completed during the parent study each time the children received vincristine every three months during year two of therapy. Patients were followed prospectively for evaluation of vincristine-associated neuropathy throughout the course of their therapy. Study nurses conducted the assessment using the Total Neuropathy Scale - Pediatric Vincristine (TNS©-PV) assessment tool following protocol training by the neurologists. Data from year 2 of the parent study was obtained for this secondary analysis. IRB approval was obtained for the parent study and for the secondary analysis. All children included in the secondary analysis were undergoing active ALL treatment and receiving vincristine.

Measures

Two measures were used during this secondary analysis. The measures will be presented and discussed below.

Demographics

Chart reviews collected patient demographic information. Age was recorded in years and sex was recorded as male or female. Race was recorded as White or non-White.

Modified Total Neuropathy Score Pediatric Vincristine (mTNS©-PV)

The mTNS©-PV measure was used in this analysis. This tool was modified by removing two original items of constipation and hoarseness from the TNS©-PV. The mTNS©-PV was used to evaluate 77 children ages 5 to 18 years old who were receiving vincristine. The mTNS©-PV is discussed in the text and table (Table 4.1) below.

The modified Total Neuropathy Score - Pediatric Vincristine (mTNS©-PV) measure quantifies subjective numbness, tingling, neuropathic pain, vibration sensibility, and temperature sensibility and it objectively measures muscle strength, and deep tendon reflexes. For the mTNS©-PV each item is scored on a 0 to 4 scale, with higher cumulative scores indicating more severe neuropathy. Internal consistency reliability was supported with a Cronbach's alpha coefficient of 0.84 (Lavoie Smith et al., 2013). The mTNS©-PV is responsive to change over time based on weekly assessment scores from baseline to week 15 (Lavoie Smith et al., 2013). PN prevalence is operationalized as a score of 4 or higher on the mTNS©-PV. Children with a TNS-PV score (range 0 to 28) $\geq$ 4 were defined as having VIPN (Lavoie Smith et al., 2013). This cut point was based on finding that 5% of normal pediatric controls have a ped-mTNS (a different TNS© variant) score of four or higher, and no normal controls had scores $\geq$ 5 (Gilchrist & Tanner, 2013; Lavoie Smith et al., 2013). Data using this measure was evaluated to answer the study aims at months 12, 15, 18, 21, and 24.

The development stage of each child can affect their ability to report their symptoms using the mTNS©-PV (Lavoie Smith et al., 2013). Children in this study were asked what their worst subjective sensory symptom was (i.e., numbness, tingling, neuropathic pain) and where the location of the symptom was (e.g., toes to midfoot, midfoot to ankle, ankle to knee, upper extremities). In addition, the children were assessed for temperature sensibility by placing a cold tuning fork on their skin and asking them to report where the temperature sensibility was reduced or absent (e.g., toes to midfoot, midfoot to ankle, ankle to knee, upper extremities). Vibration sensibility was assessed with a 128 Hz weighted tuning fork placed on bony prominences beginning at distal extremities. The patient was asked to report when the vibration was no longer sensed. The nurse would then determine if the vibration sensibility was reduced or absent in

certain locations (e.g., toes to midfoot, midfoot to ankle, ankle to knee, upper extremities). Self-reporting of the symptom implies perception of the presence of the symptom.

Deep tendon reflexes (i.e., ankle, patellar, triceps, brachioradialis, biceps) were assessed by the nurse using a reflex hammer. The reflexes were evaluated as ankle reflex reduced, ankle reflex absent, ankle reflex absent/others reduced, or all reflexes absent. The nurse evaluated strength through flexion/abduction exercises to parts of the child's body (i.e., toe extension/flexion, ankle dorsiflexion, hip flexion, hand grip, thumb abduction, wrist extension, arm abduction) and rated this strength as mild weakness, moderate weakness, severe weakness, or paralysis through resistance.

Approach to Missing Data

The secondary data set had missing data which can compromise inferences if missing data is not handled appropriately. Overall, there was 25% missing data points for the secondary data set. The first step in missing data analysis is to decide if the missing data is missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR). Missing at random is defined as missingness that is related to other measured variables in the analysis model (Baraldi & Enders, 2010). This is the most likely reason for the missing data. Children and adolescents may not be willing to participate with the nurse collecting data and age is a variable in the model. Based on secondary data set being examined, one child had a relapse during their treatment. Death was not recorded in any of the 77 children. This would not account for 25% missing data.

When data is found to be MAR, prediction of missing values can be based on the participants with complete data sets (n = 27; Jakobsen et al., 2017). Multiple imputation is considered to be superior and more powerful approach compared to other missing data

techniques such as deletion or single imputation approaches because it produces unbiased estimates for both MCAR and MAR data (Baraldi & Enders, 2010). Multiple imputation, using a regression equation generated from the 27 complete data sets, was used to create five full data sets, each containing different imputed values. These data sets were then analyzed for estimates of the means and covariances to construct a set of regression equations that can predict missing data. Bayesian estimation principles were used to generate new estimates of the means and covariances which adds a random residual term to each of the resulting estimates. This process developed imputed values for the missing values.

Aim for the Study

For Aim 1, patient and treatment characteristics were explored of children with ALL suffering from VIPN at 12 months (i.e., race, sex, age, VIPN at 12 months) to assess if any were associated with VIPN at 24 months based on the cumulative score of the mTNS©-PV. To characterize the independent variables (i.e., age, sex, and race, VIPN at 12 months), an ordinary least squares (OLS) multiple regression was conducted by calculating the average mTNS©-PV score at 24 months as the dependent variable. Age, sex, race, and VIPN at 12 months were independent variables.

Analysis

Descriptive statistics (frequencies, means, and standard deviations) were computed. With 77 participants, there was 80% power to detect a 0.75 effect size, if the type I was controlled at 60% (Lavoie Smith et al., 2015). The effect size was defined as the difference between the 12-month and 24-month cumulative mTNS©-PV scores divided by the standard deviation (Lavoie Smith et al., 2015).

Ordinary least squares regression models were used to test the hypothesis of demographic and treatment characteristics as predictor variables on the mTNS©-PV score at 24 months due to the nonnormality of the data. This method approximates coefficients using bootstrapping, which does not assume a normal distribution. Variables for the model were standardized using IBM SPSS (Version 26) to create z-scores for each variable. Interaction effects and main effects were tested. A *P*-value of 0.05 was considered as the threshold for statistical significance.

Model 1 included a full model containing main effects of patient and treatment characteristics and interaction terms. Model 2 included the main effects. Model 3 included the main effects model excluding the mTNS©-PV score at 12 months. Model 4 was an optimized model by stepwise forward and backward selection. After subject-matter experts reviewed the regression results, in the context of the data, it was believed that the relatively small sample size of non-White children in the study may misrepresent the impact of race on the response for the data. Outcomes were contrary to what is known about race in the literature. Two additional models were constructed. Model 5 retained non-White children but removed race as a predictor. Model 6 removed race as a predictor but additionally removed the one complete observation from a non-White child that had influential values. Model 7 was completed using complete case analysis (n = 27) to compare and contrast to models optimized with completely imputed data (n = 77).

Results

A total of 289 assessments were performed on 77 children during their second year of treatment. Of those children, all were able to provide multiple mTNS©-PV scores over the second year. Table 4.2 presents sample demographic characteristics based on the total number of assessments performed in the second year. Using data from those providing complete modified

TNS©-PV scores (n = 77), there were nearly equal assessments performed on males (51%, n = 39) and females (49%, n = 38) and most were performed on Caucasian (88%) children. The mean number of mTNS©-PV assessments conducted on each child was 3.2. The mean age was 8.3 years, with a range at baseline of 5 to 18 years.

When exploring the ordinary least squares multiple regression model, main effects and interaction effects were analyzed with a backward selection process of variables. Each model was tested on the data after multiple imputation was used to complete the dataset and then for all 82,160 possible combinations. For small and non-parametric data, this is a way of assessing model stability. Model 1 was a saturated model that included demographic and treatment characteristics as predictor variables and interaction effects. Adjusted R squared which describes the amount of variability for each model was calculated and analyzed during the backward stepwise approach. The Akaike Information Criterion (AIC) is one of the most widely used methods for choosing a "best approximating" model from several competing models given a particular data set with a lower number indicating better model fit. AIC was analyzed with each model change as well. Model 2 has no interaction effects with a higher AIC value and less variability explained by the model. Model 3 has a very low adjusted R^2 value accounting for only 20% of the variability of 24 month VIPN. This indicates that VIPN at 12 months is a critical predictor of VIPN at 24 months (Table 4.3). It also appears that gender, race, and age were important predictors in these models as either main effects or as interactions. Overall the models were quite good (Table 4.4). It was also shown that sub-setting the data by complete cases showing non-zero symptom scores at 24 months dramatically improved model fit and solved the non-normality issues.

After exploratory analysis, Model 1 was shown to have the best model fit based on the adjusted R squared and AIC value. The next step was to optimize Model 1 with a stepwise approach. Table 4.5 is a summary of the *p* values demonstrated during each stepwise approach to optimize Model 4. Model coefficient estimates indicate that Caucasian individuals are less likely to experience elevated symptoms at 24 months than African American individuals. Model coefficient estimates also show that there is roughly a 1 unit increase in estimated VIPN score at 24 months for every 1 unit increase in VIPN score at 12 months. Table 4.6 indicates that VIPN at 12 months is dependent on sex to predict VIPN at 24 months which indicates that sex most likely has a moderating effect on VIPN. Twelve month VIPN is shown to be a strong predictor of 24 month VIPN and contrary to previous literature, non-White children had more severe VIPN. After subject-matter experts reviewed the regression results, in the context of the data, it was believed that the relatively small sample size of non-White children ($n = 9$) in the study may misrepresent the impact of race on the response to VIPN at 24 months. The literature indicates that African American children are fast metabolizers of vincristine and are less likely to get VIPN (Renbarger et al., 2008).

Due to the concern for misrepresentation of the impact of race on the response to VIPN at 24 months, two further models were developed using OLS modeling with backward selection. The first approach, Model 5, was to retain the nine nonwhite children but remove race as a predictor. The second approach was to remove race as a predictor but also remove one highly influential complete observation from a nonwhite participant which is Model 6. Removal of this patient improved the resulting fit and altered estimates in Model 6. Table 4.6 presents the coefficient table with standard errors and p values for Model 6. This model has a significant interaction effect between male sex and 12 month VIPN but no main effects were demonstrated

as a result of the interaction effects. Ordinary least squares regression was evaluated using complete case analysis (n = 27) to compare the results with the analysis of data using multiple imputation. The results were very similar indicating an interaction effect between male sex and VIPN at 12 months but no main effect findings (Table 4.7).

Discussion

This is the first study to examine the second year of treatment and therefore adds to the science by providing a more comprehensive understanding of VIPN beyond year one ALL treatment reported in the literature. Further, these findings are based on a valid and reliable measure of VIPN, rather than an adverse events measure used primarily in clinical care for dose adjustment. However, the data was non-parametric with many values compressed around zero. It is possible that subtle subclinical nerve injury is not being detected based on the mTNS©-PV. Further refinement or development of a new VIPN measurement tool may be needed.

These results show that VIPN at 12 months and female sex are positively associated with VIPN at 24 months as an interaction effect with females having higher VIPN at 24 months. Due to this interaction effect, main effects of female sex and VIPN at 12 months as predictor variables were not assessed. No other interaction effects were identified in the analysis. Previous studies evaluating sex as a predictor variable have been inconclusive.

Age was not identified as a predictor of VIPN during year two. The relationship between age and VIPN has been tested in ten studies of which seven studies found no association. Three earlier studies reported significantly higher prevalence of VIPN in older children during the first year of ALL treatment (Ceppi et al., 2014; Diouf et al., 2015; Lavoie Smith et al., 2015). These findings are consistent with the majority of studies that have looked at age and VIPN.

VIPN at 12 months has not been evaluated previously as a predictor of VIPN at 24 months. The 12 month VIPN score is based on vincristine exposure during year one. Theoretically, VIPN at 24 months would be the result of the exposure to vincristine over the previous 2 years. Therefore the 12 months VIPN score is not independent of the VIPN score at 24 months. However, VIPN at 12 months was not a predictor of VIPN at 24 months. If nerve regeneration were to occur during year 2 of ALL treatment, then we could expect some improvement in mTNS©-PV scores and VIPN at 12 months would not predict later VIPN scores.

Race was not found to be associated with VIPN during year two. The findings for this secondary analysis indicated that African American children developed worse VIPN compared to Caucasian children. The sample was very skewed with 68 Caucasian children and nine African American children. Previously five studies investigated the relationship between VIPN and race (Anghelescu et al., 2011; Diouf et al., 2015; Kishi et al., 2007; Renbarger et al., 2008). A significant relationship between race and VIPN was demonstrated in four studies (Anghelescu et al., 2011; Diouf et al., 2015; Kishi et al., 2007; Renbarger et al., 2008), reporting that Caucasian children were at higher risk of developing VIPN than children of other origins. African American children have been shown to not develop VIPN because they have CYP3A5 allele which produces CYP3A5 enzyme and quickly metabolizes vincristine therefore African American children do not have neurotoxic affects the way Caucasian children do (Egbelakin et al., 2011; Renbarger et al., 2008). Only one study did not demonstrate a significant relationship between race and VIPN during year one of treatment for ALL however there was a significantly higher percentage of Caucasian children (88%) in the study (Lavoie Smith et al., 2015). As a result of these findings, race was removed as a predictor for VIPN in the ordinary least squares

model. Future studies with a normal distribution of race should investigate race as a predictor of VIPN.

In adults who develop peripheral neuropathy during cancer treatment, older age, higher body mass index, comorbidities, premature birth, higher cumulative doses of chemotherapy, and poorer functional status have been shown to be predictive of nerve damage (Miaskowski et al., 2017). Diabetes was also shown to be predictor of neurotoxicity during cancer treatment (Ottaiano et al., 2016) although two other studies have found no such link (Pereira et al., 2016; Simon et al., 2017). In children, many of the potential risk factors of VIPN have not been fully investigated. A prospective research design with additional predictor variables would be important as next steps for research using a large data set.

Due to the lack of identified risk factors, children undergoing treatment for ALL should be monitored closely at each clinical visit over the course of year two and interventions to mitigate VIPN should begin during year one. Trending the patient from year one to year two may give the most insight into VIPN severity during year two. Safety for the children during the second year of treatment as a result of sensory deficits should also be addressed by caregivers and the nurses.

Future studies should investigate genetic polymorphisms that may be able to provide more specific predictive factors for risk of VIPN. An increased risk of VIPN incidence and severity is associated with low-expressors' of cytochrome P450 enzyme CYP3A5 in children with ALL compared to high expressor counterparts (Egbelakin et al., 2011). Gene ABCB1 is known to alter risk of neurotoxicity (Brigo et al., 2012). Lastly, the genetic deletion of sterile apla and TIR motif (SARM1) containing protein has been shown to dramatically protect axons from degenerating after axotomy in mice (Geilser et al., 2016). Blocking this pathway has been

shown to prevent the development of VIPN thus patients who are low-expressors' of SARM1 may develop less VIPN.

None of the predictor variables in this study were significantly associated with VIPN. These findings support previous research. Next steps would be to investigate additional treatment characteristics during year two that may be able to shed light on the risk factors for VIPN. Identifying risk factors for VIPN can help nurses to improve their surveillance for peripheral neuropathy in children undergoing treatment.

Limitations

As with many secondary data analyses, this study has limitations. The data was not collected prospectively thus analysis was limited to the variables collected in the main parent study. The incompleteness of data made this study challenging to analyze. There were only 27 individuals that represented complete cases. The sample size was relatively small. A larger prospective trial would possibly elucidate additional statistically significant differences among the children experiencing VIPN during year two of treatment. The sample size had limited non-Caucasian races. The non-normality of the response, specifically compression around zero, is typically associated with data due to a limited ability to detect and measure subtle "near zero" effects. Lastly, while attempts were made to avoid parent by proxy data, a small portion of the data may have been provided by parents if the child did not understand a question.

Conclusion

Patient and treatment characteristics of children being treated for ALL at 12 months were not independently associated with worsening VIPN at 24 months. This is the first study to investigate demographic risk factors and VIPN characteristics during the second year of treatment for ALL. Further prospective studies investigating additional treatment and disease

characteristics with large sample sizes are needed to continue to investigate VIPN during year two of ALL treatment.

APPENDIX

Table 4.1

Modified Total Neuropathy Score©-Pediatric Vincristine (mTNS©-PV; Cornblath et al., 1999; Lavoie Smith et al., 2013)

Symptom	0	1	2	3	4
Worst subjective symptom (tingling, numbness, or pain)	None	Toes to midfoot, excluding heel	Midfoot to ankle	Extend above ankle to knee; no upper extremity involvement	Above the knee and upper extremity symptoms
Temperature sensibility	Normal	Absent/reduced from toes to midfoot	Absent/reduced from midfoot to ankle	Absent/reduced above ankle to knee	Absent/reduced above the knee or in lower and upper extremities
Vibration sensibility	Normal	Absent/reduced from toes to midfoot	Absent/reduced from midfoot to ankle	Absent/reduced above ankle to knee	Absent/reduced above the knee or in lower and upper extremities
Strength	Normal	Mild weakness, able to overcome resistance	Moderate weakness, can overcome gravity but not resistance	Severe weakness, cannot overcome gravity	Paralysis
Tendon reflexes	Normal	Ankle reflex decreased	Ankle reflex absent	Ankle reflex absent, others decreased	All reflexes absent

Table 4.2

Sample Demographics (N = 77)

Variable	*n*	%	*M*	*SD*
Age			8.3	3.82
Sex (*N = 77*)				
Female	38	49		
Male	39	51		
Race				
White	68	88		
Non White	9	12		

Table 4.3

Exploratory Models for Ordinary Least Squares Multiple Regression of the Mean Score of the mTNS©-PV - Patient/Treatment Characteristics and Association of VIPN at 24 months (N=77)

Exploratory Models	Adjusted R^2	AIC
Model 1 24 month VIPN = sex + race + age + 12 month VIPN + (gender:12 month VIPN) + (race:12 month VIPN) + (age:12 month VIPN)	0.7978	143.2
Model 2 24 month VIPN = sex + race + age + 12 month VIPN	0.6948	153.8
Model 3 24 month VIPN = sex + race + age	0.2006	241.0

Note. VIPN, vincristine-induced peripheral neuropathy

Table 4.4

Model 4: Optimization of Model Using Backward and Forward Stepwise Approach for Ordinary Least Squares Regression

Model 4 Steps	Adjusted R^2	AIC
1. 24 month VIPN = sex + race + 12 month VIPN + (gender:12month VIPN)	0.7840	141.78
2. 24 month VIPN = sex + race + age + 12 month VIPN + (gender:12 month VIPN) + (age:12 month VIPN)	0.8166	140.10
3. 24 month VIPN = race + age + 12 month VIPN + (age:12 month VIPN)	0.8135	132.64
4. 24 month VIPN = race + 12 month VIPN	0.5987	130.96
5. 24 month VIPN = sex + race + age + 12 month VIPN + (gender: 12 month VIPN)	0.8420	130.30
6. 24 month VIPN = sex + race + 12 month VIPN	0.6332	127.21
7. 24 month VIPN = sex + race + age + 12 month VIPN + (age:12 month VIPN)	0.8557	124.03
8. 24 month VIPN = sex + age + 12 month VIPN + (age: 12 month VIPN) + (sex: age) + (sex:12 month VIPN)	0.7378	125.26

Note. VIPN, vincristine-induced peripheral neuropathy

Table 4.5

Summary of Coefficient P-Values for Ordinary Least Squares Optimization of Models

Model 4	Intercept	Sex Male	Race White	Age	12 month VIPN	Sex Male: 12 month VIPN	Age: 12 month VIPN
24 month VIPN = sex + race + 12 month VIPN + (gender:12 month VIPN)	0.00	0.52	0.00		0.00	0.01	
24 month VIPN = sex + race + age + 12 month VIPN + (gender:12 month VIPN) + (age:12 month VIPN)	0.00	0.85	0.00	0.41	0.30	0.09	0.16
24 month VIPN = race + age + 12 month VIPN + (age:12 month VIPN)	0.00		0.00	0.19	0.19		0.01
24 month VIPN = race + 12 month VIPN	0.00		0.00		0.00		
24 month VIPN = sex + race + age + 12 month VIPN + (gender: 12 month VIPN)	0.00	0.63	0.00	0.17	0.00	0.00	
24 month VIPN = sex + race + 12 month VIPN	0.00	0.15	0.00		0.00		
24 month VIPN = sex + race + age + 12 month VIPN + (age:12 month VIPN)	0.00	0.19	0.00	0.18	0.26		0.00

Note. VIPN, vincristine-induced peripheral neuropathy

Table 4.6

Ordinary Least Squares Model with Race Excluded as Predictor Variable with Completely Imputed Data (N=77)

Optimized Model Excluding Race	Estimate	SE	t value	Pr(>|t|)
(Intercept)	1.4063	1.2094	1.1628	0.2547
Sex Male	-1.5912	1.5788	-1.0079	0.3221
Age	-0.1710	0.1346	-1.2702	0.2145
12 Month VIPN	0.6197	0.4051	1.5299	0.1373
Sex Male:Age	0.2562	0.2000	1.2812	0.2106
Sex Male:12 Month VIPN	-0.5620	0.2611	-2.1520	0.0402
Age:12 Month VIPN	0.0323	0.0308	1.0486	0.3033

Note. VIPN, vincristine-induced peripheral neuropathy

Table 4.7

Ordinary Least Squares Model with Race Excluded as Predictor Variable with Complete Case Data (N=27)

Optimized Model Excluding Race	Estimate	SE	t value	Pr(>|t|)
(Intercept)	1.5076	1.2105	1.1728	0.2603
Sex Male	-1.6101	1.5885	-1.0178	0.3335
Age	-0.1802	0.1340	-1.3002	0.2350
12 Month VIPN	0.6209	0.4150	1.5309	0.1475
Sex Male:Age	0.2674	0.2300	1.2914	0.2208
Sex Male:12 Month VIPN	-0.5807	0.2718	-2.2501	0.0454
Age:12 Month VIPN	0.0450	0.0315	1.0435	0.3123

Note. VIPN, vincristine-induced peripheral neuropathy

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CHAPTER 5: DISSERTATION SUMMARY: FUTURE NURSING PRACTICE, RESEARCH, AND POLICY

Introduction

The persistent and enduring experience of peripheral neuropathy (PN) has been identified as an area needing further research. PN is a troublesome symptom which can significantly impact the lives of pediatric cancer patients. There are a limited number of studies that investigated PN during the first year of treatment for acute lymphocytic leukemia (ALL) (Argyriou et al., 2012; Gilchrist et al., 2017; Kanbayashi et al., 2010; Lavoie Smith et al., 2015; Toopchizadeh et al., 2009). There are no studies that describe the experience of PN over the second year of treatment for ALL.

The purpose of this dissertation was to examine peripheral neuropathy (PN) in children with acute lymphocytic cancer during their second year of treatment and determine what factors are associated with VIPN during year two. This three manuscript dissertation addressed significant gaps in the literature. First, a review of the literature was completed to evaluate available measurement tools for chemotherapy-induced peripheral neuropathy (CIPN). Next, PN was characterized over time as measured by the cumulative score of the modified TNS©-PV (1–20; higher = more severe) monthly at 12, 15, 18, 21, and 24 months based on a retrospective sample of 77 children with ALL. In addition, this research identified the relative contribution of type of nerve pathway (sensory, motor, or sensory/motor) to the total VIPN score at 12, 15, 18, 21, and 24 months according to the modified TNS©-PV subscales. The sensory/motor pathway was clearly identified as the highest contributor to the mTNS©-PV score at all five time points. Finally, this research explored if any of the patient or treatment characteristics (i.e., race, sex, age, VIPN at 12 months) were associated with VIPN at 24 months after beginning treatment

based on the cumulative score of the modified TNS©-PV. The current chapter (Chapter 5) provided a summary of the three manuscripts and discussion regarding findings, interpretations, limitations, missing data, and implications for future nursing practice, research, and policy.

Utilizing the Symptom Management Model for Peripheral Neuropathy Research

The Symptom Management Model (SMM) is used in nursing research to identify gaps in symptom management, assess for management barriers, develop and implement interventions, and target future areas of research (Dodd et al., 2001). The overarching principal of the SMM involves effective symptom management that requires all three dimensions of the model (i.e., symptom experience, management strategies, and outcomes) to be considered. There are complex, multi-directional relationships in the SMM that are considered. This theory was an appropriate guide for the dissertation research, as the SMM provided a framework that encompasses key aspects of the PN experience including the symptom experience and outcomes. Use of this framework allowed for a reliable assessment of PN to be performed in order to provide new knowledge to the field that did not previously exist.

For this dissertation, the original model was adapted to represent the concept of PN in children undergoing ALL treatment. The variables being tested fit well within the model and multiple relationships within the components of the model were tested. A secondary analysis using prospective, longitudinal data was conducted to gain knowledge on the patient's experience of PN during year two of ALL treatment, since this had not been previously reported. The adapted PN SMM was developed based on the SMM to display the unique factors influencing the experience for this population. In the future, this model can be used to develop more refined measurement for PN and intervention trials that can affect modifiable variables influencing the child's experience of PN.

The adapted PN SMM guided the literature review examining CIPN tools used in pediatric clinical practice and research. In order to measure PN within the symptom experience component of the model, measurement tools were identified that could measure the subjective symptoms as well as the objective signs of PN. To date, there is no 'gold standard' measurement tool used for PN in children for research or clinical practice. In addition, there are no valid and reliable instruments that are patient-reported for CIPN in children. Several factors impede effective CIPN assessment in children in the research setting (e.g., children's difficulty describing symptoms, providers' lack of time, research assistants' lack of confidence to assess CIPN; Lavoie Smith et al., 2014). Given the dearth of evidence regarding the incidence, severity, trajectory of CIPN, and the characteristics of CIPN in children during the second year of treatment, this time period has not been well-described.

The lack of progress is related to the lack of a universally accepted comprehensive measurement tool that is reliable, valid, and clinically feasible to assess pediatric populations (Gewandter et al., 2019; Kandula et al., 2016). Comparing studies among CIPN clinical trials is difficult and impedes meta-analysis (Gewandter et al., 2019; Kandula et al., 2016). With a gold standard measurement tool, common data points could be used and researchers may be able to detect phenotypic variability of CIPN at differing disease stages (i.e., early or advanced stages) and treatment stages (i.e., induction phase, consolidation, delayed intensification, maintenance phase).

Chapter 2 (Manuscript 1)

For this dissertation, the literature review identified five available pediatric CIPN tools. The Ped-mTNS is useful as a research and clinical tool in children receiving neurotoxic chemotherapy. However, one of the items is a pinprick test which can cause psychological

distress to young children. The modified TNS©-PV is currently the best tool for research and clinical tool to screen and monitor children for PN; however, it lacks age specificity for the various developmental stages.

To further refine pediatric reporting of CIPN, the mTNS©-PV could be adapted to incorporate age-specific measures, much in the same way that pediatric PROMIS measures were developed for other symptoms. A collaborative of PN researchers may need to convene to provide expert input and oversee psychometric testing for age-specific measurement tools for CIPN. Understanding how PN and the nerve pathways change during year two may assist conceptually with the tool development.

Chapter 3 (Manuscript 2)

Chapter 3 characterized the changes in PN in a retrospective sample of children with ALL using the cumulative score of the modified TNS©-PV (range 1–20; higher = more severe) monthly at 12, 15, 18, 21, and 24 months and identified which nerve pathway contributed to a higher PN cumulative score using the subscales of the modified TNS©-PV at the aforementioned time points. This study was guided by the adapted PN SMM which tested the relationship between the PN symptom experience and outcomes (i.e., PN prevalence, PN severity).

This study found that 56% of children continued to experience PN during the second year of treatment for ALL as assessed by the TNS©-PV which is less than year one prevalence rates (78%) and VIPN severity remained stable throughout year 2 of treatment. The mean TNS©-PV score during the first year of treatment for ALL was 4.08 (14.5%) with a range from 0 to 28. The mean mTNS©-PV score at 24 months was 3.2 (16%) with a range from 0 to 20 indicating that severity of VIPN was unrelenting during the second year of ALL treatment. These findings validate that VIPN does not resolve during year two of ALL treatment. A decrease in prevalence

may be the result of less frequent (every 3 months) vincristine administration during year 2. The sensory/motor nerve pathway had the highest mTNS©-PV score during the second year, followed by the sensory and motor nerve pathways. Based on the findings from Chapter 3, it is clear that sensory and motor pathways should be the focus of prevention and management strategies to be tested during year two of ALL treatment.

These findings add to the science regarding year two of treatment due the use of rigorous and validated methods used to quantify PN in this population. This study included a moderate but acceptable sample size (289 assessments in 77 children) from a parent study with a longitudinal study design. Use of the modified TNS©-PV enabled a more accurate VIPN description and trajectory than previously published reports using smaller sample sizes and cross-sectional designs. Although this is the first study investigating the trajectory of VIPN over the second year of treatment for ALL, the findings indicate that VIPN is a persistent and bothersome symptom that would benefit from intervention studies focused on treatment strategies. Validating these findings in a large, prospective study would provide additional evidence to support these results.

Chapter 4 (Manuscript 3)

Chapter 4 determined if patient characteristics or treatment characteristics of children being treated for ALL were associated with more severe VIPN during the second year of treatment. This study was guided by the PN SMM and tested the relationship between the components of person and outcomes in the model. Person was operationalized as a child with ALL undergoing treatment for ALL. The variables of sex, race, age, and VIPN at 12 months were examined to see if they were associated with VIPN at 24 months.

The results for Chapter 4 demonstrated that age, sex, race, and VIPN at 12 months were not associated with VIPN score at 24 months. These findings are consistent with the majority of studies that have looked at age, sex, and race as predictor variables.

Race was not found to be associated with VIPN during year two. The findings for this secondary analysis indicated that African American children developed worse VIPN compared to Caucasian children. The sample was very skewed with 68 Caucasian children and 9 African American children. Previously a significant relationship between race and VIPN was demonstrated in four studies (Anghelescu et al., 2011; Diouf et al., 2015; Kishi et al., 2007; Renbarger et al., 2008), reporting that Caucasian children were at higher risk of developing VIPN than children of other origins. As a result of these findings, race was removed as a predictor for VIPN in the ordinary least squares model. Future studies with a normal distribution of race should further investigate race as a predictor of VIPN.

Sex was not found to be associated with VIPN during year two. The results of this secondary analysis are consistent with previous studies finding no association between sex and VIPN.

Lastly, VIPN at 12 months was not associated with VIPN at 24 months. This has not been investigated before therefore there are no findings for comparison, and these findings were not as expected. It would seem that vincristine exposure at 12 months would potentially impact VIPN at 24 months. Studies with large sample size and a valid and reliable VIPN measurement tool should re-test this relationship.

This is the first study to investigate risk factors for VIPN during the second year of treatment for ALL. Since no risk factors for predicting VIPN were identified, further investigation of risk factors is critical to the development of neuroprotective strategies and

treatment strategies for VIPN. Further prospective studies with large sample sizes are needed to continue the investigation of VIPN during year two of ALL treatment. The ability to identify at-risk children for VIPN during the second year of treatment for ALL will help nurses predict which patients to monitor closely during year 2 of treatment.

Limitations

There are several limitations of this research. The literature review only included articles published in English, which could lead to a publication bias. In addition, the tools were limited to measuring CIPN thus the results could not be applied to other types of PNs including diabetes or HIV treatment.

A secondary analysis was completed for Chapters 3 and 4, thus analysis was limited to the variables collected in the parent study. Additional data would have created a broader and more inclusive investigation of the year two symptom experience. In addition, some of the data were collected as parent-by-proxy since some of the children may not have understood the questions being asked or were not able to answer for other reasons. The sample size was moderate and was predominantly Caucasian thus making the generalizability of the results limited. This sample size was adequately powered to detect differences in the outcomes; however a larger sample size with normally distributed data would have been preferred. Non-parametric tests were used to complete the analyses for Chapters 3 and 4. The missing data in this study was approximately 25%. This is a large amount of missing data therefore multiple imputation was used. For this reason, three analyses were completed to see if this imputation method mirrored other analyses including data with no missing data and data with some missing data (missing 1 or 2 months of data). All three analyses were similar and thus the multiple imputation analyses was supported.

On the other hand, many of the limitations provided educational opportunities. A well-established symptom science model was applied and adapted to align the specific variables of this work. Knowing more about year two of PN among children, provides a foundation for refined assessments and interventional work. Finally, the work needed to impute missing data and the use of non-parametric tests provided exposure to new analytic methods.

Implications of Dissertation

Implications for Nursing Research

This dissertation adds to nursing knowledge by addressing the paucity of published papers on the second year of treatment for children experiencing PN. Second, the mTNS©-PV measure provided highly specific neuropathy phenotype data that has not been obtained and utilized previously for year two in a pediatric ALL population. The analyses indicates that assessment of motor, sensory, and sensory/motor neuropathy is warranted during year two of treatment for ALL. The data had a large amount of "stacking on zero" which would indicate that the measurement tool used in this study may not have detected sub-clinical VIPN. Additional tool development may be needed for future studies. A standardized, age-specific tool to report pediatric PN would be helpful to capture children and adolescent symptom experience across a variety of illnesses. Third, describing the incidence, severity, and temporal patterns of sensory, sensory/motor, and motor neuropathy can inform researchers about the stable yet unresolved progression of neuropathy which can lead to intervention development for children with VIPN. Fourth, this study provided detailed information on the timing to implement and test targeted interventions. VIPN begins during year one of treatment for ALL and was found not to resolve during year two of ALL treatment. Interventions should be implemented during year one and continued during year two of ALL treatment.

Implications for Health Policy

The Oncology Nursing Society (ONS) research agenda for 2019 to 2022 include the overarching priorities of symptom science, health disparities, and palliative and psychosocial care in oncology. More specifically, one of the goals is to characterize symptom variability in presentation, describe the trajectory across various patient populations, and examine factors such as age, sex, and race that may influence patient responses to therapy. This agenda closely aligns with this dissertation work. In addition, the 21st Century Cures Act was passed by Congress in December 2016 providing $1.8 billion in funding for the Cancer Moonshot Research Initiatives (NCI, n.d.). This initiative is to increase symptom management research to improve outcomes for pediatric and adolescent cancer survivors and develop new therapies. The results of this dissertation demonstrate that PN is a persistent and bothersome symptom during year two of ALL treatment. The ONS research agenda and the Cancer Moonshot Research Initiative can now support researchers to develop management strategies since PN does not resolve during year two.

Lastly, the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act of 2018 was passed by Congress in June of 2018 to accelerate and optimize development of childhood cancer treatments which may have less treatment-related toxicities (NCI, 2019). By understanding the prevalence and severity of PN during year two of ALL treatment, new treatment options can be tested and recommended if they in fact do provide an improved toxicity profile.

Implications for Practice

Childhood cancer care involves a risk-based model incorporating active treatment, routine health care, and a personalized plan for surveillance and extended screenings in addition to management of late effects of cancer treatment. Health outcomes research has provided strong

evidence linking PN during the first year of ALL treatment with vincristine to adverse outcomes and this evidence allows clinicians to identify potentially at-risk children (Lavoie Smith et al., 2015). So nurses can do what for at risk children?

Patients with ALL or survivors of ALL are already a vulnerable population, and the development of PN can be devastating to these individuals. Preventing further impairment should be a priority for nurses and other healthcare providers. New age-specific pediatric tools to evaluate PN severity and functional status need to be developed. Understanding the trajectory of the PN and the characteristics that place ALL children at increased risk will give clinicians valuable information to anticipate the clinical course.

By assessing PN early and proactively treating functional impairments, nurses can prevent falls and injuries among patients with PN. Interventions should include the entire healthcare team including physicians, nurse practitioners, nurses, physical therapists, occupational therapists, and home health services. Patient and provider education is vital in preventing injuries and other complications of PN as well as maintaining patient's quality of life and physical functioning. Nurses can advocate for their patients when they understand the trajectory and implications of the toxicities. Future research should focus on identifying additional risk factors for PN, examining differences in symptom presentation and physical functioning between boys versus girls with VIPN, Black versus White children with VIPN, and finding more effective means of prevention and treatment.

Implications for Education

Undergraduate nursing students need to understand the developmental, physical, psychosocial, and cognitive challenges of peripheral neuropathy. As described in Chapter 1, this condition can have profound effects on the child. Understanding this dynamic condition of PN

and how it affects the child's development are important concepts for nursing students. In addition, this dissertation informs nurses about the PN experience during year two of ALL treatment, the importance of fall risk assessments for these children, and the lack of treatment strategies available. Observing and learning about potential strategies for dealing with this troublesome condition could guide future scientific investigations. Lastly, it is important to educate nurses to inform patients receiving vincristine about potential symptoms and functional impairments that may result from their treatment.

For chemotherapy-induced toxicities, patient and nursing education are paramount to successful symptom management. Nurses who fail to prioritize toxicities cannot adequately inform and counsel patients about the true risk to benefit ratio of the treatments they are considering. Additionally, the lack of knowledge about PN makes it difficult for patients and parents to prepare themselves mentally for potential challenges and hurdles that await them. Patients who are educated on the frequency and severity of neuropathy resulting from a specific chemotherapy agent are impacted and may be able to choose regimens that minimize their toxicities. This implies that nurses must strive to educate patients and families in the case of ALL in a more detailed fashion so that they might make the best possible decision for their therapy.

Future Research

Future research must focus on developing interventions for the management of moderate to severe VIPN in children. Research into pharmacologic and non-pharmacologic VIPN prevention and treatment methods have been relatively futile. However, there are new novel prevention and treatment approaches actively being studied in adults that may provide insight into the development of pediatric interventions (Kleckner et al., 2018; Stechmann et al., 2018). For adults, potential interventions have included massage, acupuncture, foot baths, progressive

walking, and resistance exercise programs (Kleckner et al., 2018). Aerobic exercise, mindfulness, occupational therapy, and physical therapy have also been evaluated as potential self-management strategies for reducing the impact of CIPN symptoms (Argyriou et al., 2014).

Among children in this study, the sensory/motor pathway was identified as being the most severe during the second year of treatment; therefore the development of treatment strategies to help children cope with sensory and motor impairment is needed. The sensory pathway is associated with balance and coordination; whereas, the motor pathway is associated with severe muscle weakness and declining physical function. With these functional alterations in mind, aerobic and resistance exercise, occupational therapy and physical therapy may be the most promising strategies to reduce PN.

Another area of interest would be to understand which aspects of VIPN are the most troublesome for daily living in children with ALL such as psychosocial factors. Further investigation into the psychological, social, and developmental characteristics of ALL patients with VIPN could close an important gap in the science. Understanding how children are affected by PN during different developmental and cognitive stages should guide intervention development. To help address this need, measurement tools and management strategies need to be age-appropriate.

While multiple avenues are possible to improve quality of life as children go through treatment for ALL, post-treatment assessments may also shed light on useful interventions. Examining children after treatment is completed would elucidate whether nerve regeneration or other types of neural compensation occur and if physical therapy or other management approaches facilitated such a recovery.

Summary

In summary, this body of work has contributed to science by completing a review of the literature for pediatric chemotherapy-induced peripheral neuropathy measurement tools, characterized the longitudinal trajectory of peripheral neuropathy during year two of ALL treatment, and described the specific pathways in order to design interventions for the management of PN. This work also identified factors associated with VIPN at 24 months so children with ALL may benefit from enrollment in future intervention studies. This work was successfully guided by the adapted PN SMM, and will provide the framework for additional research studies on PN among children with ALL. Finally, prevention, early recognition, and interventions for VIPN are imperative to ensure children can remain on the most effective chemotherapy regimen and improve the neurological function and quality of life of childhood cancer survivors.

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