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Recovery of Nerve Function after Treatment for Childhood Cancer

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ABSTRACT

Background

Chemotherapeutic agents have been the backbone treatment for pediatric cancers. Unfortunately, a number of the chemotherapy medications have potential side effects, including chemotherapy-induced peripheral neuropathy (CIPN). To measure the extent of CIPN, the Pediatric Modified Total Neuropathy Score (Peds-mTNS) has been shown to be a reliable and valid measure of CIPN in school-aged children and is associated with relevant functional limitations. However, future research is needed to describe the recovery of CIPN in children and adolescent cancer patients after treatment has ended.

Purpose

To analyze the trajectory of recovery for CIPN in school-aged children diagnosed with non-CNS cancers and to evaluate if diagnosis and treatment impact CIPN type and recovery.

Methods

Forty-seven subjects ranging in age from 5-18 years undergoing chemotherapy with vincristine or a combination of vincristine and intrathecal methotrexate participated in the study. Peds-mTNS scores as well as standardized balance and hand function measures were taken on treatment (at the anticipated peak of CIPN) and then 3 and 6 months post treatment. Descriptive statistics and one-way repeated measures ANOVA were run to compare subjects over time (on treatment, 3 months, and 6 months post). A 2-way

repeated measures ANOVA was run to compare mean Peds-mTNS scores for each diagnostic group over time.

Results

18 subjects with Acute Lymphoblastic Leukemia (ALL), 8 with Wilma' tumor, 14 with non/Hodgkin's lymphoma and 7 with other non-CNS cancers were evaluated. Across all subjects (n=47), Peds-mTNS scores decreased significantly over time (on treatment 9.5± 4.4, 3 months 5.8 ± 4.7, 6 months 4.3 ± 4.0, $p < 0.001$), indicating an improvement in CIPN. Overall effect size, with Partial Eta Squared, was found to be large (0.609). Greatest individual measure effect size was shown in deep tendon reflex (.659). Of the diagnostic groups, patients with Hodgkin's lymphoma were found to have significantly less improvement on the Peds-mTNS than subjects with leukemia (6.4 ± 0.7 vs 2.2 ± 0.6 at 6 months, $p<0.05$), even though their treatment time was shorter in duration and they received less vincristine.

Conclusion

Overall, the trajectory of recovery for pediatric cancer patients was found to be positive, resulting in significant improvements in CIPN symptoms over time post-treatment, although patients with Hodgkin's lymphoma were more likely to have residual neuropathy.

RESEARCH ADVISOR FINAL APPROVAL FORM

The undersigned certify that they have read, and recommended approval of the research project entitled

RECOVERY OF NERVE FUNCTION AFTER TREATMENT

FOR CHILDHOOD CANCER

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in partial fulfillment of the requirements for the Doctor of Physical Therapy Program

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Chapter I: Introduction and Literature Review

In 2014 it was estimated that 15,780 new cases of pediatric (ages 0-19 years) cancer occurred in the U.S.[1] From this same set of statistics, the National Cancer Institute, it was determined that nearly 2,000 of them would die from their malignancy.[1] Given the high occurrence in the pediatric population, the focus of this study is on the most common types of cancer. These are, in order of rate of prevalence: leukemia (including both acute lymphoblastic and acute myelogenous subtypes), Hodgkin's lymphoma, non-Hodgkin's lymphoma, and Wilma' tumor. Patients affected by cancers of the brain, although also prevalent, were not included in the study. This is partially because the complex circuitry of the brain warrants its own study, but also because other neurological deficits due to the tumor location in this population can confound the evaluation of symptoms.

Leukemia is a cancer of the bone marrow and blood, and can be split into two main subgroups: Acute Lymphoblastic Leukemia (ALL) and Acute Myelogenous Leukemia (AML). ALL is the most common type, affecting 3 out of 4 patients with leukemia. ALL is a fast growing cancer of the lymphoid cells in bone marrow. The population that is most frequently diagnosed with ALL is Caucasian females. AML accounts for the remainder of patients diagnosed with leukemia. This type of cancer is fast growing and appears in the myeloid cells that create leukocytes, erythrocytes, and platelets.[2] Treatment for leukemia includes chemotherapy, radiation, and blood transplants or bone marrow transplants.[3] The cause of leukemia is unknown at this time.[3] The 5-year survival rate for ALL is 80%, while the survival rate for AML is 60-70%, as

stated by the American Cancer Association.[2] Survival rates for both ALL and AML have increased with the advancement in the medical treatment for pediatric cancer.[2]

Wilma' Tumor, first discovered by Dr. Thomas Wilma, presents on the kidneys most often in a unilateral growth but can affect both kidneys. It is common in young children 3-4 years old with a higher prevalence in African-American females. A primary sign of the tumor may be swelling or hardening of a child's abdomen.[2] The most common treatment for Wilma' tumors is surgical removal combined with chemotherapy (before or after the surgery), and usually radiation therapy is only used in more advanced cases.[2] According to the American Cancer Association the survival rate for Wilma' Tumor after surgery is 90%.[2]

Non-Hodgkin's Lymphoma (NHL) is more common in older teens, with a higher diagnosis rate in Caucasians and males.[2] This type of cancer affects the lymph system, made up of the spleen, thalamus, tonsils/adenoids, and lymph nodes. A primary risk factor for this cancer is a weak immune system either from birth or developed over a period of time.[2] The signs and symptoms of NHL vary depending on the location of the cancer. Some patients may show swelling in the lymph node areas; this can cause fluid to build up and may cause pain. Key signs include fever, chills (mostly at night), and unexplained weight loss. Chemotherapy is the main form of treatment with this cancer; the use of surgery and radiation are used on a smaller scale.[2]

Hodgkin's Lymphoma, also known as Hodgkin's disease, is different from NHL in its growth and treatment. The population more at risk for developing Hodgkin's are males in their 20's from a higher socioeconomic status.[2] Hodgkin's lymphoma typically

occurs in the upper portion of the body in areas of the neck, chest, and underarms. The cancerous cells develop from mutated B-lymphocytes, named Reed-Sternberg cells after the doctors that discovered them.[2] Hodgkin's types can be split into two main groups: Classic Hodgkin's disease and Nodular Hodgkin's disease. While the latter only makes up 5% of the cases, Classic Hodgkin's disease makes up 95% of cases and has four subgroups. The most prevalent of these subtypes is Nodular Sclerosis Hodgkin's disease, and makes up 60-80% of classic Hodgkin's diagnoses.[2] The varying types of Hodgkin's lymphoma can be differentiated by viewing the cancer cells under a microscope.[2] The two most common forms of treatment for this type of cancer are chemotherapy or radiation.

With the advances in the medical treatment of cancers, more people are reaching the 5 year survival marker than in years past. As stated by the National Cancer Institute, children diagnosed with cancer had a 58.1% of reaching the 5 year survival marker in 1975-77. The rate increased to over 80% in 2010,[1] a statistic echoed by the American Cancer Society. With more children surviving cancer, health care providers are becoming more aware of the long-term functional deficits showing up in survivors.

Treatment/Medications

As previously mentioned, the survival rates of pediatric cancer patients have continued to climb steadily over the years. These increases are largely due to the use of multimodal therapy, using active chemotherapeutic agents.[4] Chief among these agents are vincristine, and intrathecal methotrexate, which will be the key medications focused upon

in this review. Other agents that are also used less frequently are taxanes, bortezomib, thalidomide, and a variety of platinum compounds.

Vincristine is a medication that directly affects cells by depolymerizing microtubules, which are responsible for a cell's overall structure. Vincristine is primarily used for the treatment of: leukemia, Hodgkin's and non-Hodgkin's lymphoma, Wilma' tumor, neuroblastoma, and rhabdomyosarcoma.[4] It can be administered intravenously via PICC line, catheter, or cannula.[6] It is considered a "backbone" of therapy in both the initial (induction) and secondary (consolidation) phases of pediatric malignancies, even though neurotoxic side effects are common."[7] In adults it has been shown to cause abnormal function of A-beta, A-delta, and C-fiber sensory afferents.[8]

Methotrexate attacks cancer cells by protein-mediated endocytosis. It can be used intrathecally to treat cancer cells hidden in the central nervous system (CNS). Evidence suggests that several mechanisms of methotrexate play a role in both its therapeutic and neurotoxic effects, including direct effects on intracranial endothelial cells and brain white matter, as well as immunologic mechanism.[9] A spectrum of clinical syndromes may occur: radionecrosis, necrotizing leukoencephalopathy, mineralizing microangiopathy with dystrophic calcification, cerebellar sclerosis and spinal cord dysfunction. Neuropsychological and neuroendocrinological damage are the most common categories of outcome/sequelae.[9] There is also increasing evidence that children that undergo cancer treatment and become long-term survivors, may be at increased risk for the development of secondary CNS tumors, possibly as a result of the aforementioned treatment.[9]

Side Effects

Many side effects manifest during, and after, the treatment of cancer in children, and can be both psychological and physical. At the time of diagnosis, and upon the advent of treatment, certain symptoms appear to be comparably more prevalent. They are also seen as a greater burden, though this burden decreases through the course of recovery.[10] The symptoms reported as the most problematic during treatment are: emotional distress, fatigue, nutrition, and pain; the latter often being described as the worst.[10] Some less prevalent, but still distressing, symptoms include: difficulty breathing, swallowing, and difficulty with urination.[10] Fatigue, one of the more prevalent symptoms, has been found to interfere with child development,[11] as it can severely limit activity during treatment (however, this may be reduced with therapy).

Physical activity in survivors of childhood cancer is an area that has received more attention in recent research. A survivor of childhood cancer may be limited in their physical activity (walking, jumping, reaching, bending) secondary to neurological and musculoskeletal deficits.[12, 13] Although a child may attempt to resume a normal amount of physical activity, they will likely have difficulties keeping pace with same aged peers without a cancer diagnosis. Hoffman et al. compared the physical performance of survivors of childhood cancers to the siblings of the survivors and found similar levels of activity in each group. However, the survivors performed at a lower ability than the siblings of the survivors.[12] This is pertinent because the result of this decreased quality of performance may lead to decreased leisure physical activity. For example compared to controls, adult survivors of childhood ALL reported less leisure time physical activity.[8]

The attempt at increasing physical activity may improve a patient's quality of life, but it is not enough to overcome all of the physiological changes that occur with intense chemotherapy and long term hospitalization from cancer.[12] For example, children with ALL often present with decreased balance compared to age-matched control subjects.[8] Balance dysfunction is not the only impairment present after intense chemotherapy; survivors of cancer may also demonstrate poor mobility, decreased sensation, decreased endurance, and growth failure due to the decreased production of growth hormones.[14,15]

Side effects from cancer and treatment of cancer do not end after a patient goes into remission. Many individuals have long term residual side effects from both the cancer and the intense treatment. Children are at greater risk for side effects from cancer therapy because the treatment tends to target rapidly growing cells.[13] In a 2010 study by Haddy and Haddy, 75% of participants with pediatric cancer survivors had one or more late side effects.[15] This finding is consistent with an investigation by Hoffman et al. in which two-thirds of long-term cancer survivors presented with at least one chronic condition.[12] These include: respiratory symptoms, changes in liver function, hyperglycemia, hypothyroidism, and altered renal functioning.[15]

Furthermore, survivors of childhood cancers can be at greater risk for many types of conditions and deficiencies. These include, but are not limited to: early mortality, second malignancies, immune system suppression, infectious disease, endocrine deficiencies, cardiac impairments, pulmonary dysfunction, sensory loss, gastrointestinal problems, neurocognitive deficits, genitourinary disorders, musculoskeletal abnormalities, and infertility.[13] Any of these subsequent side effects and risk factors can

lead to secondary limitations including lack of educational attainment, impaired emotional well-being, and reduced physical performance. Ultimately, this may affect a child's daily routine, school attendance, and/or interpersonal relationships.[13]

A 2011 study published in *Oncology Nursing Forum* examined improvement of the 6 Minute Walk Test (6MWT) in pediatric patients with ALL, lymphoma, or solid tumor during chemotherapy treatment. The study found that those with ALL had the greatest improvement on the 6MWT compared to those with lymphoma or solid tumors.[11] Although patients with ALL showed the most improvement on the 6MWT, these patients also reported more fatigue, pain, and insomnia, overall when compared to patients with other hematological malignancy (e.g. AML). Patients with ALL have also been found to have lower quality of life, physical function, and cognitive function than patients with AML.[4]

In addition to physical side effects, psychological symptoms are often common during treatment due to the initial shock of diagnosis and the burden of being treated for cancer. Patients receiving treatment for hematological malignancies are subjected to increased frequency of anxiety and depression, though both are often undetected.[4] Other psychological problems include: fear, uncertainty, as well as mood and cognitive issues.[16] The latter can be present in both older and younger patients, but they are not as severe as the emotional symptoms that may be present.[4]

Chemotherapy-Induced Peripheral Neuropathy

The effects of chemotherapy treatment for childhood cancers may lead to a number of unfortunate side effects, as previously described. One of the potentially most

devastating effects is the changes that result in the peripheral nervous system. Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose-limiting neuropathy defined as, "Any injury, inflammation or degeneration of the peripheral nerves because of the administration of a chemotherapeutic agent."[3] CIPN can be manifested in any of the three functional divisions of the nervous system: sensory, motor, and autonomic nerves resulting in damage within and around the neuron. It can occur at the axon, cell body, and myelin level.[17] The mechanism of damage and symptoms that occur depend on the type of nerve affected and specific chemotherapeutic agent used. Commonly used neurotoxic agents causing damage to nerve fibers include, but are not limited to: platinum-based compounds, vincristine and vinca alkaloids, taxanes, epothilones, bortezomib, and thalidomide.[19, 3]

Within the nervous system, two types of peripheral nerve fibers exist, small and large. Motor axons are large fibers, myelinated, fast conducting, and directly control muscles. Typically, these motor neurons have the ability to reinnervate and sprout in order to survive the effects of chemotherapeutic agents, thereby resulting in more mild symptoms and less frequent occurrence.[16] Sensory and autonomic axons are characterized by small fiber nerves, unmyelinated, slower conduction, and sense pain, temperature, and control autonomic function. The cell bodies of these peripheral sensory neurons lie in the dorsal root ganglion (DRG), outside the protective blood-brain barrier, thereby leading to an increased vulnerability for damage from chemotherapeutic agents. Also, the DRG is highly vascularized, being supplied by a large number of capillaries, thereby increasing the permeability for toxic compounds.[16]

Therefore, CIPN has been shown to first manifest in small sensory fibers leading to changes in sensation, paresthesia, dysesthesia, cold sensitivity, tingling, numbness, proprioception, vibration, and reflex changes.[20] It occurs in a length dependent manner, affecting the longest axons first and spreading proximally, also known as a "stocking and glove pattern."[17,16] A possible explanation for this distribution has attributed the effect to longer fibers having greater surface area; thereby putting these fibers at greater risk of exposure to harmful agents.[16]

CIPN has been shown to be dose dependent, relating to the administration of the drug and schedule of delivery (occurring within hours, days, or weeks), with the exception of cisplatin where symptoms may occur months after drug administration (coasting effect). A number of risk factors have also been identified increasing the risk for CIPN, including: heritable factors, personal, multidrug/multimodal use, radiation, and certain diseases (vitamin B12 deficiency, diabetes, hypothyroidism, and paraneoplastic diseases).[19] Although risk factors have been stated and the detrimental effects of chemotherapeutic agents noted, chemotherapy continues to the frequently used in the treatment of childhood cancers.

PT Implications

Although childhood cancer mortality rates have decreased, which can be contributed to multimodal improved therapy, a number of short-term and long-term effects are still reported.[18] These effects can be detrimental to children as they develop, in turn impacting a child and family's quality of life, risking functional decline, and additional health related complications.[12] A comprehensive understanding about patient's

symptoms is necessary for management. As stated previously, "two-thirds of long term survivors will develop ≥ 1 chronic condition related to prior therapy."[12] It is critical for health care providers to acknowledge the symptoms children with cancer are experiencing. Research has begun to improve symptoms in those receiving chemotherapy, but it has been structured towards chemotherapy-related nausea and vomiting.[12] As previously noted, these symptoms are not the only chemotherapy side effects children are experiencing.

Physical therapy (PT) can play a role in providing rehabilitative services to help with improving function, adapting needs, finding compensatory strategies, and managing structural and functional losses related to disease processes.[19] Unfortunately, little research has been done to show the effects it may have on children receiving chemotherapy for childhood cancers.[19] Montgomery et al. looked at 5+ year survivors from the Childhood Cancer Survivor Study (CCSS) addressing the use of PT and chiropractic services and association with health-related quality-of-life (HRQL). They compared PT and/or chiropractic utilization between survivors and siblings, and by diagnosis, treatment and demographic characteristics; associations between chronic disease, PT/chiropractic use, and HRQL.[19] Their results showed a slightly higher percentage of survivors reported using chiropractic (12.4%) than PT (9.2%) services, yet both are minimally utilized.

This is interesting to note, as many children receiving chemotherapy treatment show both short and long term effects potentially limiting their physical function. A poorer HRQL measure was also noted in those who used PT/chiropractic services. They

attributed this to the possibility that survivors with more severe late effects may utilize services more in comparison to those with less effects, in turn reporting a poorer HRQL.[19] However, it is important to note that these results cannot be generalized to all children with childhood cancer. This study has offered good insight into how many additional services are utilized, or underutilized, and the role PT can play in optimizing physical function.

In light of current underutilization, it is important to educate patients on the role PT can have in treating children with childhood cancers. Neuropathy is a common side effect of chemotherapeutic agents used for treatment of childhood cancers. Specifically, CIPN is the most widely reported and has been the focus of research efforts. However, effective management of symptoms can be difficult to approach as a result of the broadly described symptoms and neurotoxic effects across studies.[16] Therefore, the National Comprehensive Cancer Network (NCCN) task force created an outlining of recommendations for the possible prevention, diagnosis, and management of neuropathy.[16]

Treatment starts with evaluating patients. Evaluations should be done at baseline, throughout and following the course of treatment. It involves subjective and objective measures; however, no gold standard has been established for CIPN. The lack in consistency in rating and patient reported symptoms adds to the difficulty of treating CIPN. Objective measures include EMG, nerve conduction, quantitative sensory tests, and other additional imaging techniques, but these have shown poor correlation with subjective reports by patients.[16] History and physical examination should also be included

to account for possible exposures impacting the patients functioning. A combination of symptom characteristics, past medical history, associated comorbidities, and detailed description of dosing regimen should all considered. Specifically for the physical exam, the NCCN recommends, "assessment of sensory abnormalities, deep tendon reflex dysfunction, motor weakness, pain characteristics, autonomic symptoms, and most importantly, functional impairment."[16] Finally, a number of physician based grading systems and patient-based instruments have been developed to determine severity of neuropathic symptoms. The NCCN outlines a number of additional recommendations for health care providers while treating CIPN: constant assessment, pain assessment tools, questions based around ADLs, and referral to specialist if needed.

Unfortunately there is no single treatment option specifically for CIPN, therefore, treatment typically includes managing symptoms with protective agents, TENS, and complementary alternative medicine. In a randomized control trial, Mokhtar et al. attempted to determine the effectiveness of glutamic acid in reducing neurotoxicity of vincristine, as it had been shown to modify the effects in preclinical animal trials. The following effects were used to measure toxicity: achilles and patellar tendon reflexes, paresthesia, and increased frequency of constipation.[7] The onset of neurotoxicity was much later in the glutamic acid group compared to the placebo group, but further research is needed to help determine the efficacy of toxicity-reducing co-treatments.

The NCCN also outlined the role PTs can play; PT intervention can assist with managing functional deficits including balance, strength, sensory loss, and performing ADLs. Balance activities can begin with static standing and moving to advance

manipulation of objects done statically and dynamically. Manipulation of activities can be done by masking visual input, changing size of objects, changing speed of activities done, and changing surfaces. Daily strengthening programs can be established to improve lower extremity strength, gait training, reduce fall risk, and assist with ADLs. These programs have shown beneficial results for improving strength.[16]

Gait training specifically should include observation of footwear, gait deformities, balance ability, strength, endurance, and how patients respond in complex conditions. The NCCN reports benefits of training with bodyweight support systems as well.[16] Overall, therapeutic interventions need to be focused on the patient as a whole. Due to the many adverse events that may occur throughout treatment, it is important to understand the causes for decline in function may be due to multiple variables. Education, advice, coping strategies, modifications, adaptive equipment, and safety are all areas recommended to be discussed with patients throughout their treatment process.[16]

Hoffman et al. found similar results when they compared the physical performance of children with childhood cancers to their siblings. Physical performance was measured by using a handheld dynamometer, 6 min walk, and TUG. Their results showed that even though children with childhood cancer had poorer results on performance measures, they participated in regular physical activity as much as their siblings.[12] In light of this, further referral may be necessary for these patients, for assessment of physical function and continued exercise programs, which can promote an active lifestyle and prevent ongoing decline.

Purpose of Study

As previously stated, pediatric cancer is a highly prevalent disease, with a growing survival rate, due to rapidly evolving treatment techniques. However, with chemotherapy being essential to treatment, CIPN is unfortunately a common consequence, with effects ranging from discomfort to severe debilitation. We do know that the effects of CIPN may continue to influence a child's quality of life long after the treatment of their cancer. It is also apparent that the severity and frequency of adverse events heavily depend on dose, duration, schedule of administration, cumulative effects of additional drugs, and preexisting dysfunction.[16] Yet despite high overall occurrence, data on neuropathic toxicity appears fragmented and there has not been a research focus on chemotherapeutic medicine.[16]

Most of the existing research lies in the adult population, which though it may be informative as to the late effects, ignores that treatment combinations (including medication types and dosage) may differ in pediatric populations and lead to different impact on the nervous system. There also appears to be a lack of evidence in regard to standardization of reporting CIPN-like symptoms; it may be difficult for a school age child to report their symptoms. As an example of the gaps in current literature, Ness et al. provided evidence of chemotherapy-related neuropathic symptoms and functional impairment in adult survivors. 21 out of 531 participants tested positive for both motor (17.5%) and sensory (20%) impairments and demonstrated functional impairment in 6MW, TUG, and SOT.[13] However, they failed to provide description of PT throughout

the course of chemotherapeutic treatment, and the information is only very broadly applicable to a pediatric population, if at all.

A feasible measure of CIPN has been created; the mTNS, which demonstrates greater sensitivity than other existing measures.[8] However, more research is needed utilizing this tool in order to create normative values and cut off scores in order to be used as a clinical measure of CIPN symptoms.[8] Further research is also needed when looking at the effects of chemotherapy and peripheral neuropathies in pediatric cancers longitudinally. It needs to start at diagnosis and be observed throughout the course of treatment.[14] In addition, it would be beneficial to know what mechanisms are directly responsible for these effects, and what interventions can be implemented for the treatment of CIPN.

Therefore, the key purpose of our study is to evaluate the trajectory of recovery for CIPN at three and six months post-treatment, in children with ALL, lymphoma, and non-CNS solid tumors. As previously mentioned, brain tumor diagnoses were excluded as they present with their own unique deficits that could potentially confound our research. Our secondary aim was to evaluate and quantify the recovery of balance and manual dexterity post-treatment. Finally, we wanted to identify if there were any significant differences between diagnostic groups.

Outcome Measures

The most common outcome measure used clinically for children and adolescents with CIPN is the Common Terminology Criteria for Adverse Events (CTCAE).[21] CTCAE objectively measures adverse events that occur after cancer treatment in 26

different body systems. Sensory and motor neuropathy is used to measure the severity of CIPN.[21] Recent evidence has shown that there are limitations to the CTCAE when determining CIPN. For example, the CTCAE is less sensitive to small changes in reflexes because it only measures the deep tendon reflex of the ankle, rather than both the ankle and the knee. It also does not measure a wide range of large and small diameter sensory fibers, resulting in misleading information about the severity of CIPN.[12] The limited range of sensory fiber sizes tested with the CTCAE inspired the search for a better-equipped outcome measure for the assessment of CIPN.

An alternative test used in the past is the Total Neuropathy Score (TNS), which was initially developed for assessing peripheral neuropathy in adults with diabetes.[12, 13] The TNS includes subjective and objective information about sensory, motor, and autonomic symptoms which may be present.[12] For the upper and lower extremities, pin sensation is assessed via a Medipin and vibration sense via a Biothesiometer. Motor function is objectively measured via strength testing of the great toe extensors, ankle dorsiflexors, finger abductors, and wrist extensors. The achilles and patellar deep tendon reflexes are also assessed.[12] Autonomic symptoms are subjectively measured through questions in the patient interview.

The TNS has been found to be reliable (interrater=0.94; intrarater=0.97) and valid for adults, however, changes were required prior to using the tool for children and adolescents.[12,13] In order to collect subjective information regarding symptomatology, the patient interview was altered to be read aloud to the children and the language was simplified. Furthermore, the scoring rubric was evaluated and deemed appropriate by

neurologists, experts of clinical practice of oncology, and pediatric physical therapists. The new variation of the TNS for children being treated for pediatric cancer is called the Pediatric Modified Total Neuropathy Score (peds-mTNS). The entire peds-mTNS, patient interview and five part neurological exam, takes about ten minutes.[12]

In order to assess the peds-mTNS more thoroughly, a pilot study was conducted by Gilchrist et al. in 2009. The study, published in *Rehabilitation Oncology*, evaluated the performance of the peds-mTNS by 20 participants diagnosed with leukemia, lymphoma, or solid tumors. Specific findings of this study helped to direct and validate the development of the peds-mTNS. For example, during the interview, 15 of the 20 reported either a sensory or motor symptom, or both. Although the most prevalent symptom was sensory deficits, objective information from pin and vibration sensitivity did not correlate with the subjective sensory findings. Additionally, neither pin sensitivity nor vibration sensitivity correlated with one another, indicating that each of those are independent variables which need to be included within the peds-mTNS. It is important to note that neither ceiling nor floor effects were found when using the peds-mTNS. Two limitations of the peds-mTNS are that autonomic neuropathy, which includes thermoregulation, digestion, and orthostatic hypotension, is not assessed objectively. The second limitation is peds-mTNS is not appropriate for children younger than five years old.

The peds-mTNS has been shown to be more valid and reliable than the CTCAE. The sensory clinical exam in the peds-mTNS includes assessment of both small diameter fibers. Small fiber testing is accomplished via the pin sensibility portion of the

neurological exam, and large diameter fibers by the vibration and deep tendon reflex portion of the outcome measure. The CTCAE does not include the same wide of range of fiber size tested.[12] The CTCAE and the peds-mTNS were compared by Gilchrist et al. in 2013. This study demonstrated that the CTCAE failed to detect light touch deficits in 40% of the participants, vibration sensory deficits in 20%, and was incorrect in the 15% of the population who reported that motor neuropathy deficits were not present. The CTCAE also had a low sensitivity of .2. When directly comparing the peds-mTNS and CTCAE, there was no correlation between any of the components, except for strength scores. The study suggests that the Peds-mTNS is more sensitive than the CTCAE at detecting CIPN.

Chapter II: Methods

Subjects

All subjects were approached for participation in the study while at outpatient appointments at a children's oncology clinic. Inclusion criteria were children ages 5 to 18 years old, a new diagnosis of leukemia, lymphoma or solid tumor (Wilms', Rhabdomyosarcoma, neuroblastoma), receiving chemotherapy treatment using Vincristine or Cisplatin, English-speaking subject and guardian, and viewed as appropriate for study by their physician, nurse or physical therapist. Exclusion criteria were previous cancer diagnosis or relapse, CNS tumor, developmental or other neuromuscular disorder, non-English speaking subject or guardian, and upper or lower extremity amputations or limb deficiency.

The institutional review board at Children's Hospitals and Clinic of Minnesota reviewed the recruitment material, consent forms, and testing procedures for the study. Parents of each subject completed a demographic questionnaire that includes questions about age, sex, racial background, and past medical history. A trained clinical research associate extracted information about cancer diagnosis and treatment from medical records. This information included: diagnosis and staging, surgical interventions, cumulative dose of each chemotherapeutic agent used, radiation treatments, and comorbid conditions.

Timing of measures

All subjects underwent the same testing procedures at 3 time points. Measures were completed during treatment, a minimum of 2 months after the start of

chemotherapy, at a time when their symptoms were anticipated to be at their peak. Specifically, children with ALL were tested at the end of the "delayed intensification" phase of their treatment, approximately 6 months into treatment. All other groups were tested between 2-3 months after the initiation of treatment. Data was again collected at 3 months and 6 months from the end of chemotherapy treatment to investigate recovery of nerve function. Subjects, who had a relapse of their cancer and required additional treatment, were excluded from the study. Therefore, subjects did not receive any treatment from the 3 month to 6 month measures.

Ped-mTNS

A clinical outcome measure for CIPN is the Total Neuropathy Score (TNS). This was initially developed for assessing peripheral neuropathy in adults with diabetes. The Pediatric Modified Total Neuropathy Score is a modified version of the TNS adapted for use in children and adolescents undergoing cancer treatment. This measure has demonstrated reliability and validity and thus was the measurement of choice for our study when looking at the effects of CIPN in school-aged children with cancer.[20]

Bruininks-Oseretsky Test of Motor Proficiency, Version 2 (BOT-2)

In addition to the 8 item Peds-mTNS measure, each subject additionally underwent the balance and manual dexterity subscales of the Bruininks-Oseretsky Test of Motor Proficiency, version 2. Both subtests were administered according to standardized protocols. The BOT-2 is designed to assess motor proficiency in children with mild to moderate functional deficits. Age and gender based scores are established for each

subtest and each age category. The standardized mean score is 15 points with standardized deviation of 5. Both the balance and manual dexterity subtests have Inter-rater reliabilities above 0.9.[22]

Data Analysis

SPSS Software was used for data analysis. Descriptive statistics was evaluated for all subject demographics. A one-way repeated measures ANOVA was run to compare all subjects over time. Effect size was evaluated by determining the Partial Eta Squared. A 2-way repeated measures ANOVA was run to compare mean Peds m-TNS total scores for each diagnostic group over time. A significant difference was indicated by a p value $< .05$ for all ANOVA data analysis. And finally, calculations were done to see the frequency of normal vs. abnormal scores for the Peds-mTNS total score, each sub-category, manual dexterity, and balance.

Chapter III: Results

There were a total of 47 subjects with 53.2% of the subjects being female. The participants in the study ranged from 5 to 18 eighteen years old and had a mean age of 11.1+/-4.099 years old. Time in treatment ranged from 57 to 512 days with a mean of 151.7 days +/- 100.1. (Table 1)

Table 1. Descriptive Statistics and Subject Demographics

	Mean	Standard Deviation	Range
Sex	Male (n=22) Female (n=25)	-	-
Age (years)	11.1	4.099	5-18
Weight (kg)	45.3	24.6	16.1-141.6
Height (cm)	144.4	27.5	40.6-196.9
BMI (percentile score)	56.98	30.5	1-99
Time in Treatment (days)	151.7	100.1	57-512

A majority of the subjects were diagnosed with ALL at 38%, followed by Hodgkin's lymphoma (30%), Wilms' tumor (17%) and other non-CNS solid tumors (15%). All of the subjects in the study received vincristine. Twenty-two subjects received both vincristine and IT methotrexate. There were a total of twenty-five subjects that only received vincristine for treatment. There were no subjects in the study that only received IT methotrexate for chemotherapeutic treatment.

A one-way repeated measures ANOVA was run in order to determine the significant change in mean Peds-mTNS scores over time. Figure 1 depicts the decrease in Peds-mTNS mean scores over time. Across all subjects, the mean scores significantly decreased between each measurement with a p value of < 0.001. The bolded black line indicates a normal score of less than 5; lower scores demonstrate less peripheral neuropathy. Therefore, at 6 months the mean score was below 5 indicating a score within normal limits. The overall effect size was found to be large at 0.609.

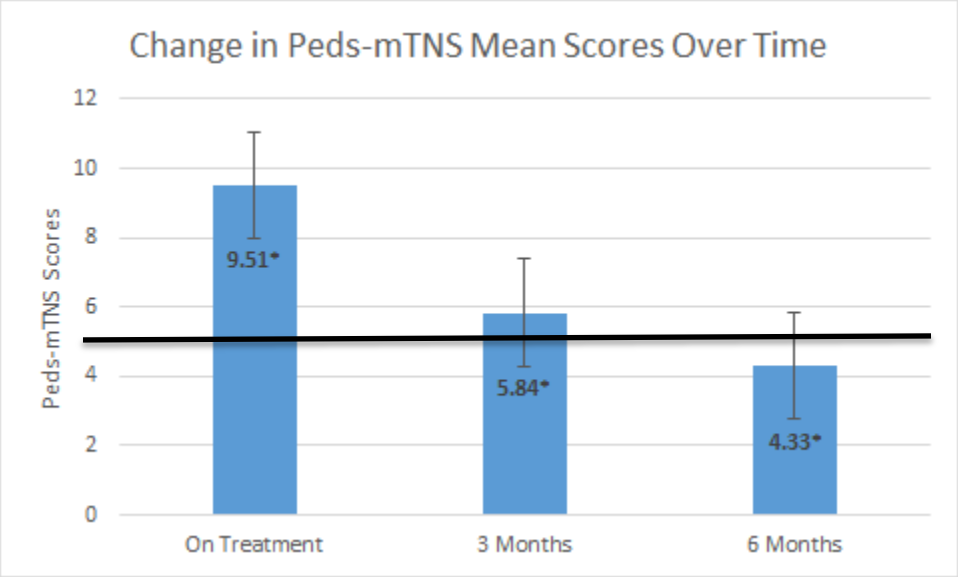

Figure 1. Change in Peds-mTNS Mean Scores Over Time

A pairwise comparison was run to find where significant differences ($p < 0.05$) occurred in the separate categories within the Peds-mTNS over time. From "On Treatment to 6 months" there was a significant difference within: motor symptoms, autonomic symptoms, right and left dorsiflexion strength, right and left great toe strength, and deep tendon reflex. From "3 months to 6 months" there was a significant difference within: lower extremity vibration, and right and left dorsiflexion strength. It was noted

that right and left dorsiflexion strength had a significant change in mean scores over both time period. Whereas, there were no significant changes in mean scores for lower extremity vibration until after 3 months post-treatment.

Table 2 shows the percentage of subjects with deficits on treatment, 3 months, and/or 6 months post-treatment. Each subscale of the Peds-mTNS total scores, BOT-2 Balance, BOT-2 Manual Dexterity, and the subjective/clinical items of the Peds-mTNS are included. There was the greatest percentage of subjects with deficits at 6 months on the BOT-2 Balance (81.1%). There were also relatively high remaining percentage of subjects with deficits at 6 months with the Peds-mTNS Total scores (37%) and BOT-2 Manual Dexterity Scores (46.7%). The categories of the Peds-mTNS with the largest percentage of subjects with deficits at 6 months include: left and right great toe strength which were 54.3% and 63% respectively, and deep tendon reflexes at 52.2%.

Table 2: Percentage of Subjects with Deficits and Group Means at On Treatment, 3 months post-treatment, and 6 months post-treatment.

Ped-mTNS Items	On Treatment		3 Month		6 Month	
	% with Deficit	Group Mean	% with Deficit	Group Mean	% with Deficit	Group Mean
Ped-mTNS Score	87.0	9.49	53.2	5.81	37.0	4.24
BOT-2 Manual Dexterity	84.4	10.4	58.7	13.54	46.7	14.76
BOT-2 Balance	95.7	7.72	89.4	9.21	81.1	10.75
Subjective Symptoms						
Sensory	29.8	0.38	17.0	0.26	10.9	0.15
Motor/Functional	55.3	0.98	23.4	0.36	23.9	0.3
Autonomic	47.8	0.96	28.2	0.45	26.7	0.43
Clinical Examination						
Light Touch UE	17.4	0.37	6.5	0.09	4.3	0.04
Light Touch LE	34.0	0.85	21.3	0.55	17.8	0.59
Pin Sensibility	46.8	0.51	44.7	0.51	33.3	0.38
Vibration UE	4.3	0.11	0	0	0	0
Vibration LE	30.0	0.68	25.5	0.7	8.7	0.28
Strength Great Toe L	89.4	1.68	61.7	0.96	54.3	0.67
Strength Great Toe R	89.4	1.79	74.5	1.09	63.0	0.83

The mean scores of the peds-mTNS for each diagnostic group decreased over time. The mean scores for subjects with Wilma' tumor and Hodgkin's lymphoma remained above the population norm indicating neuropathy. A two-way repeated measures ANOVA revealed a significant difference between means scores of ALL and Hodgkin's lymphoma with a p value of <0.05. Figure 2 depicts the change in subject mean scores on the Peds-mTNS over time by diagnosis. The black line on the graph indicates an abnormal Ped-mTNS score which is greater or equal to 5.

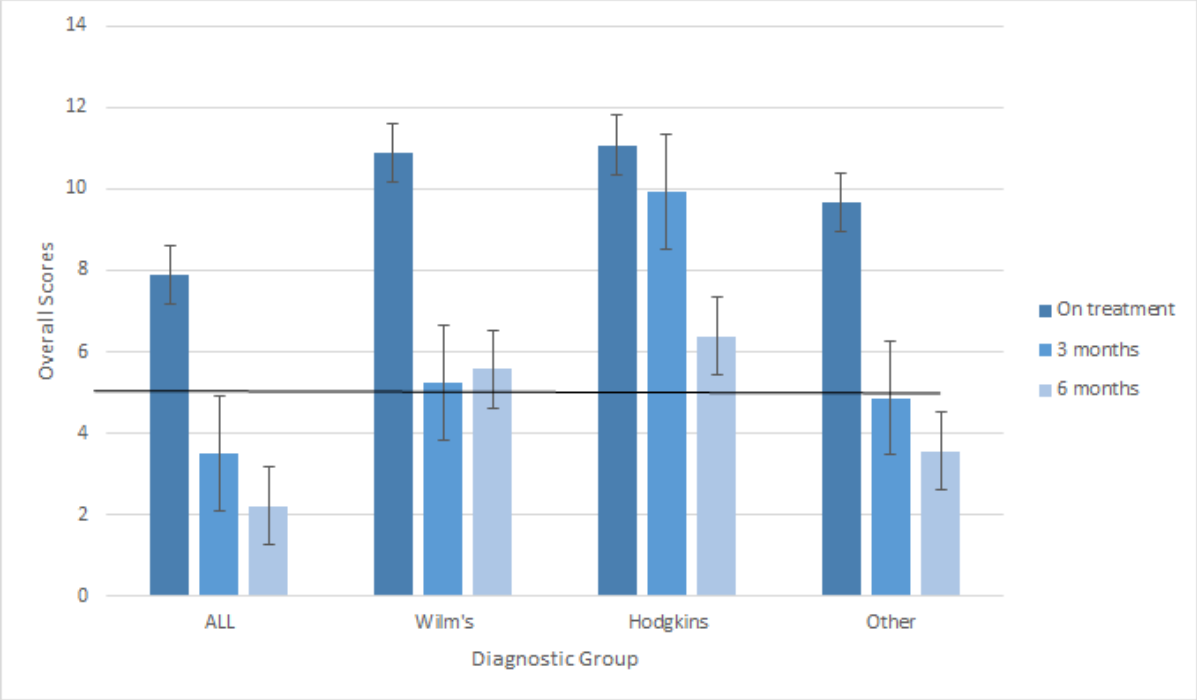

Figure 2. Change in Peds-mTNS Scores Over Time Per Diagnosis

Figure 3 is similar to Figure 2 however it displays the change in manual dexterity over time for each diagnostic group. The bolded black line once again shows the population norm score, which is 15. Therefore, those with other non-CNS tumors achieved a mean score above the population norm at 6 months post treatment. All other diagnostic groups improved over time however did not reach the population norm. A two way repeated measures ANOVA did not find any significant difference between diagnostic groups in regard to change in manual dexterity outcome measure scores.

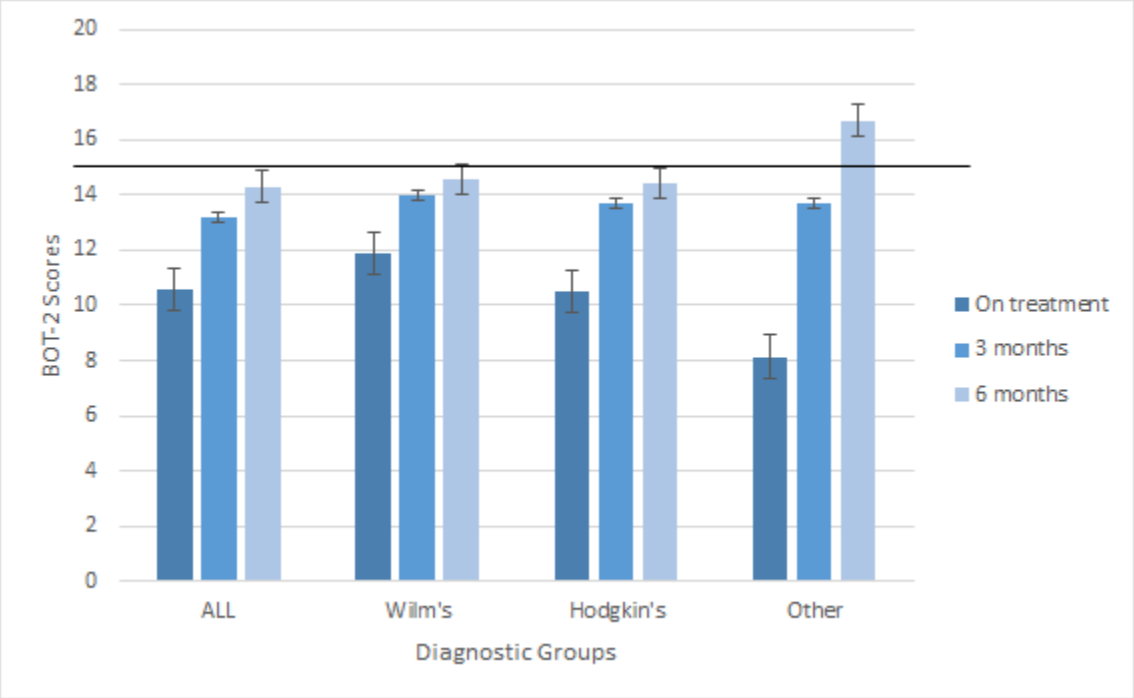

Figure 3. Change in BOT-2 Manual Dexterity Scores Over Time by Diagnostic Group

None of the diagnostic groups reached the normative value (15) on the BOT-2 balance subscale however, each group's mean scores improved over time. Those with ALL had the lowest mean score of 9.82 at 6 months. A two way repeated measures ANOVA detected no significant difference in BOT-2 balance score changes over time and between diagnostic groups. (Figure 4)

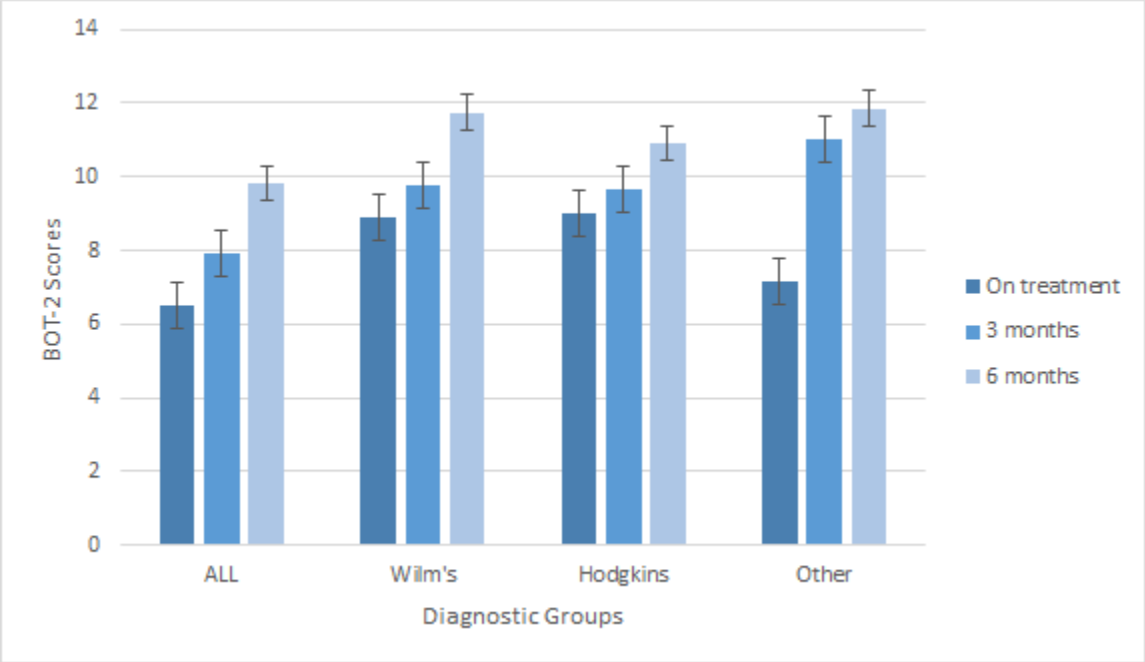

Figure 4. Change in BOT-2 Balance Scores Over Time by Diagnostic Group

In order to see what variables could have affected the subjects trajectory of recovery we looked at mean age, time in treatment, type of chemotherapeutic medication, and the cumulative dose of those medications per diagnosis. Subjects with Hodgkins lymphoma had the highest mean age (14.46+/-4.08) and those with Wilma' tumor had the youngest(7.5+/-2.20). Subjects with ALL had the greatest mean time in treatment at 802.5+/-410.96 days. The next closest mean time in treatment was the mean score for subjects other non-CNS tumors at 172.71+/-40.55 days.

All subjects with ALL received both types of medication. These patients also received the greatest cumulative dose of both medications. Those diagnosed with Wilma' tumor and Hodgkins lymphoma only received vincristine. Within the subjects that were diagnosed with another non-CNS tumor, 4 subjects received only vincristine and 3 subjects received both types of chemotherapeutic agents. (Table 3)

Table 3: Descriptive data of mean age and treatment protocol for each diagnostic group.

Diagnosis	Mean Age (SD)	Days in Treatment (SD)	Vincristine Cumulative Amount (SD)	IT Meth Cumulative Amount (SD)
ALL	9.83 (3.45)	802.5 (410.96)	53.36 (11.56)	237.83 (70.27)
Wilma' Tumor	7.5 (2.20)	157.38 (50.57)	21.17(4.23)	0
Hodgkins	14.46 (4.08)	104.58 (63.16)	10.09 (1.97)	0
Other	12.29 (2.69)	172.71(40.55)	11.93 (8.66)	53.57 (69.20)

Chapter IV: Discussion

Based on the results this study shows all group mean scores decreased significantly on the Peds-mTNS over the three data collection periods, indicating a decrease in peripheral neuropathy (Figure 4). However, it should be noted at 6 months post-treatment, 37% of subjects still presented with deficits on the Peds-mTNS (Table 2). Of those 37%, the areas of greatest deficits were found in bilateral great toe extension strength and deep tendon reflexes. When comparing the BOT-2 scores at 6 months deficits in balance (Figure 6) and manual dexterity (Figure 5) were identified. The deficits in balance, manual dexterity, deep tendon reflex and great toe extension strength could be indicative of greater residual loss to the motor system.

Table 4: Peds-mTNS data of current research subjects compared to normative values from a 2013 research study by Gilchrist and Tanner [20]

Peds-mTNS Item	Subjects (n=47)	Controls (n=41)
Sensory Symptoms	0.15	0.02
Motor Function	0.30	0.10
Autonomic Symptoms	0.43	0.46
Light Touch	0.59	0.05
Pin Sensation	0.38	0.32
Vibration Sensation	0.28	0.10
Distal Strength	0.83	0.39
Deep Tendon Reflex	1.20	0.00

The 2013 study by Gilchrist and Tanner was used to reference normative values for the Peds-mTNS.[20] It was found that the subject groups scored greater for every single item except for autonomic symptoms as seen in (Table 4). . Interestingly, deep tendon reflex scores were found to have the greatest difference between the subjects and the control groups.

When comparing across diagnostic groups for Peds-mTNS, scores for subjects with ALL and other non-CNS tumors were within normal limits at 6 months (Figure 2), indicating significant decrease in peripheral neuropathy. Those with other non-CNS tumors also had a BOT-2 manual dexterity mean score that was greater than population norms at 6 months post treatment (Figure 3). Indicating, the average subject in this diagnostic group was able to recover manual dexterityl. This differs from the BOT-2 balance scores, where none of the diagnostic groups had a mean score that reached the population norm. With this being said subjects with ALL had the best mean score at 6 months post-treatment for the Peds-mTNS, however they did not recover well on the BOT-2 balance outcome measure. Relative lack of recovery could be indicative of greater deficits in the CNS due to greater time in treatment, large cumulative dose of chemotherapeutic drugs, and the use of both, vincristine and IT methotrexate. IT methotrexate has greater potential for chemotoxic effects on the CNS due its ability to cross the blood-brain barrier.[23]

When comparing across all the diagnostic groups (Figure 2), ALL and Hodgkin's lymphoma showed statistically significant differences for Peds-mTNS mean scores over time. Subjects with ALL improved significantly more than those with Hodgkin's

lymphoma. This finding was inconsistent with expectations, as the ALL group received higher doses, multiple medications, and were on treatment far longer, as shown in (Table 3) in the results section. When examining other differences between ALL and Hodgkin's lymphoma, age differences were notable, with the ALL group being significantly younger than the Hodgkin's group. This correlation leads us to hypothesize that age-dependent neuroplasticity may play a role in the recovery from CIPN.

As stated previously research shows "⅔ of long term survivors will develop at least one chronic condition related to prior therapy."[l] Based on our results, balance and manual dexterity were affected during treatment, but balance deficits more commonly persist after treatment is complete. It is important to note that patients with non-CNS cancers may present with deficits in the aforementioned areas and these deficits may carry over into their remission and long-term recovery, which in turn may affect their continued quality of life.[24] Physical therapy can play a role in providing rehabilitative services to help with improving function, adapting needs, finding compensatory strategies, and managing structural and functional losses related to disease processes.[s]

This study had both strengths and limitations. A strength to the study is the relatively large number of subjects allowing a more reliable reflection of the subject population. The Peds-mTNS has been shown to be a valid and reliable instrument for assessing peripheral neuropathy in this subject population. A potential limitation was that data transfer to SPSS software had potential for increased errors. In order to reduce this risk, random spot checks were performed through data entry. Subject availability and the lack of controls in this study are also weaknesses.

Chapter V: Conclusion

The current literature on CIPN in this subject population states: "motor cells recover faster than sensory cells".[16] However, our study demonstrated that a greater percentage of subjects continued to have significant motor deficits at 6 months when compared to sensory symptoms. While we have discussed what we believe to be a likely course for CIPN and recovery. Other factors need to be considered as they may have affected subjects' severity of symptoms. Much of the current research has been on patients with ALL. However, our data shows that ALL subjects had the most successful recovery, and therefore it follows that patients with Hodgkin's lymphoma may benefit more from a focus of future research. The potential long-term side effects of CIPN in the pediatric population can be diminished with skilled physical therapy interventions that are researched based and individually focused.

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