PREVENTION AND IMPROVEMENT OF COGNITIVE DEFICITS IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) SURVIVORS TREATED WITH CHEMOTHERAPY: EVIDENCE-BASED INFORMATION FOR PARENTS

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ABSTRACT

This thesis summarizes what is known about the cognitive changes in childhood acute lymphoblastic leukemia (ALL) survivors treated with chemotherapy, as well as associated risk factors and intervention strategies. An educational pamphlet was developed compiling this information to serve as anticipatory guidance for parents of children diagnosed with ALL.

ALL is a cancer of the blood and bone marrow and is the most common pediatric malignancy, accounting for 25% of cancers in children under 15 years of age. Treatments are extremely successful, with survival rates of 90% for children younger than 15 years. Unfortunately, treatment side effects increase with the increase of survival rates. Treatment-related cognitive deficits occur in up to 40% of childhood ALL survivors, and is becoming increasingly common.

Results from the literature review indicate that children with ALL treated with chemotherapy have cognitive impairment in the areas of total intelligence quotient (IQ), working memory, attention, information processing speed, fine motor speed, visual IQ, verbal IQ, performance IQ, problem solving, and sequential reasoning. These cognitive problems can have a significant impact on the child’s quality of life and transition back to school after treatment. Interventions that are effective in improving cognitive outcomes include cognitive and/or problem-solving interventions.
CHAPTER 1: INTRODUCTION

Statement of Purpose

The purpose of this thesis is to summarize current knowledge about the neurocognitive changes associated with chemotherapy treatment in children with ALL, as well as related risk factors and intervention strategies. A pamphlet was created which compiles this information to provide anticipatory guidance for parents. The goal of the proposed intervention is to increase awareness of cognitive changes that occur with chemotherapy in childhood ALL patients and educate about evidence-based intervention strategies to help prevent or remediate these cognitive changes.

With increasing incidence and survival rates of childhood ALL comes an increase in the occurrence of cognitive deficits associated with chemotherapy in ALL patients. A brief overview of childhood ALL, the treatment process, treatment side effects, and the potential mechanisms of brain injury that could be related to cognitive changes will be useful in understanding the research about the cognitive deficits, risk factors, and intervention strategies which are discussed in the second chapter.

Overview of ALL Disease Process

ALL is a disease of the blood and bone marrow, and it usually progresses quickly if left untreated. In a healthy child, bone marrow generates stem cells, or immature blood cells, that become mature blood cells over time (NCI, 2016). There are two kinds of stem cells: myeloid stem cells and lymphoid stem cells. Myeloid stem cells mature into red blood cells, platelets, and myeloblasts, which then become granulocytes (a type of white blood cell) (NCI, 2016). Lymphoid stem cells develop into lymphoblasts, which further mature into one of three types of
lymphocytes, or white blood cells—B-lymphocytes, T-lymphocytes, or natural killer cells (NCI, 2016).

The development of ALL involves a series of genetic alterations involving the genes that control cellular growth, division, multiplication, and death of lymphoid stem cells or committed T- or B-lymphoblasts, resulting in the development of an abnormal cell (Esparza & Sakamoto, 2005). If an abnormal cell survives, it begins clonal expansion and leukemia consequently develops (Esparza & Sakamoto, 2005). The abnormal lymphoblasts continue to divide and multiply, but never differentiate into proper lymphocytes—they become leukemia cells (NCI, 2016). The leukemia cells do not function like normal lymphocytes and are unable to fight infection effectively. Additionally, as the number of leukemia cells increases in the blood and bone marrow, there is less room available for healthy white blood cells, red blood cells, and platelets (NCI, 2016). This often leads to infection, anemia, and abnormal bleeding (NCI, 2016).

There are two primary types of ALL: B-Cell Acute Lymphoblastic Leukemia (B-ALL) and T-Cell Acute Lymphoblastic Leukemia (T-ALL). The most common type of childhood ALL, accounting for 85% of cases in the United States, is B-ALL. T-ALL accounts for 15% of cases in the United States and outcomes are generally much poorer for T-ALL than B-ALL (Bhojwani, Yang, & Pui, 2015). There are multiple further subtypes within B-ALL and T-ALL which result from the different interactions of the aforementioned genetic alterations that occur (Bhojwani, Yang, & Pui, 2015).

**Treatment of ALL**

The primary treatment for children with acute lymphoblastic leukemia is chemotherapy. While radiation is an effective method of central nervous system-directed therapy, its effectiveness is outweighed by known adverse side effects, such as neurotoxicity and cognitive
dysfunction, and its high rates of precipitating secondary neoplasms. Thus, use of radiation is limited to the small percentage of patients with particularly high risk for central nervous system (CNS) relapse.

Chemotherapy alone is significantly less neurotoxic than cranial radiation, but also has detrimental effects on specific neurocognitive functions such as visual processing, visual-motor functioning, attention, and executive functioning (Anderson & Kunin-Batson, 2009). Childhood ALL survivors experience subtle long-term neurocognitive deficits after treatment, even in the absence of radiation treatment (Buizer, de Sonneville, & Veerman, 2008).

The types and doses of chemotherapy administered is dependent on the child’s risk status. A child’s ALL can be classified as low-, standard-, high-, or very high-risk. Risk stratification is currently determined by algorithms that evaluate genetic information such as aneuploidy (abnormal number of chromosomes in a cell) and certain genomic rearrangements, along with age at diagnosis, initial white blood cell count, CNS involvement, minimal residual disease (MRD) response (measure of residual leukemic cells in blood and bone marrow at different points throughout treatment to determine the child’s response to treatment), and subtype of ALL (Hunger & Mullighan, 2015). These algorithms have improved outcomes by enhancing the use of intensive chemotherapy regimens to avoid under- and overtreatment of patients and by limiting the use of radiation (Hunger & Mullighan, 2015).

Chemotherapy treatment consists of three phases: induction, consolidation (also referred to as post-induction), and maintenance. Induction chemotherapy generally lasts four to six weeks and involves intense treatment (Ward et al., 2014). The goal of the induction phase is to achieve disease remission. Remission is marked by observation of normal bone marrow samples and blood counts (American Cancer Society [ACS], 2015).
If remission is not achieved treatment is increased or prolonged. More aggressive chemotherapy is often followed by bone marrow transplantation to replace abnormal stem cells killed by chemotherapy with healthy stem cells. This aggressive method of treatment is commonly seen with children whose ALL is categorized as high risk at the time of diagnosis and for children whose leukemia returns after remission.

The second phase of treatment, consolidation chemotherapy, typically lasts several months and is the most intense phase of CNS-directed treatment. It is in this phase that radiation and/or bone marrow transplantation are implemented if indicated (Ward et al., 2014). If the child is still in remission after the consolidation phase, the maintenance phase begins, which lasts approximately two to three years (Ward et al., 2014).

**Side Effects of Treatment**

Side effects of ALL treatment can occur during the time of treatment and can continue after treatment has ended. Side effects that occur while treatment is still in progress are referred to as early effects (Leukemia & Lymphoma Society [LLS], 2013). These include hair loss, nausea, vomiting, fatigue, constipation or diarrhea, neuropathy (numbness, tingling, pain, and weakness in the hands and feet), and anemia, among others (LLS, 2013). Effects that occur after conclusion of treatment are referred to as late effects. These effects can be cognitive or physical, and can greatly impact a child’s learning and transition back to school, as well as their overall quality of life (LLS, 2013). Cognitive late effects are those that include thinking, learning, and memory, and are increasingly common (LLS, 2013). Cognitive late effects that occur after ALL treatment will be discussed in more depth in the following section. Physical late effects include seizures, hearing or eyesight problems, neuropathy, and need for prosthetics or a wheel chair (LLS, 2013). Some late effects manifest right away, while others take years to develop.
Cognitive Changes Associated with Chemotherapy Treatment of ALL

As mentioned previously, cognitive late effects are those affecting thinking, learning, and memory (LLS, 2013). Further research showed that children with ALL who were treated with chemotherapy have neurocognitive impairment in the areas of total intelligence quotient (IQ), working memory, attention, information processing speed, fine motor speed, visual IQ, verbal IQ, performance IQ, problem solving, and sequential reasoning (Anderson & Kunin-Batson, 2009; Duffner et al., 2014; Harila, Winqvist, Lanning, Bloigu, & Harila-Saari, 2009; Iyer, Balsamo, Bracken, & Kadan-Lottick, 2015; Lofstad, Reinfjell, Hestad, & Diseth, 2009; Peterson et al., 2008). As a result of these deficits, affected children often have difficulties in the academic areas of reading and mathematics (LLS, 2013). Other common problems include organizational issues and difficulty with comprehension (LLS, 2013). See Table of Evidence in Appendix A for a summary of recent literature on the cognitive deficits in children with ALL treated with chemotherapy.

Risk Factors for Experiencing Cognitive Deficits after Chemotherapy Treatment for ALL

Risk factors for chemotherapy-related cognitive dysfunction in children with ALL include age at diagnosis, gender, and existence of comorbidities. Additionally, certain cancers automatically put children at a higher risk of developing cognitive deficits, including ALL (LLS, 2013). Research shows that, while ALL is more common in boys, girls have worse cognitive outcomes (Anderson & Kunin-Batson, 2009). It is also shown that children who are younger at the time of diagnosis have greater deficits (Anderson & Kunin-Batson, 2009). Pre-existing comorbidities also place the child at greater risk of experiencing negative cognitive changes after chemotherapy (Castellino, Ullrich, Whelen, & Lange, 2014).
Intervention Strategies

A systematic review, by Moore, Hockenberry, & Krull (2013), reviewed five studies which discussed intervention strategies to prevent or minimize cognitive changes associated with chemotherapy. Four of the five studies tested the efficacy of cognitive and/or problem-solving interventions. The fifth study explored the therapeutic effect of a stimulant medication called methylphenidate (MPH) in improving acute neurocognitive abilities, which was found to produce significant toxicity, offsetting any therapeutic effects that may have been observed (Conklin et al., 2007). Butler et al (2008) tested a cognitive remediation program which was found to significantly improve academic performance. Patel et al (2009) tested an intervention that taught compensatory learning and problem-solving skills and was effective in improving writing skills and social functioning. Hardy et al (2010) explored the efficacy of a computerized cognitive training program and found that it significantly improved working memory. Moore et al (2012) evaluated the usefulness of a mathematics intervention which proved effective in improving mathematical problem-solving; this improvement was sustained over time. Details of these studies will be addressed in chapter 2.

Summary

The purpose of this thesis is to create a best-practice educational pamphlet for parents of children with ALL that provides all relevant information about the cognitive changes that occur in children with ALL treated with chemotherapy, as well as the risk factors and intervention strategies associated with these changes. The incidence and survival rates of childhood ALL are increasing, along with the occurrence rates of cognitive dysfunction in these survivors. It is important that parents are educated so that they can provide the necessary enriched environment,
can be aware of certain warning signs, and can effectively advocate for their child to maximize their child’s quality of life after cancer.
CHAPTER 2: REVIEW OF LITERATURE

Introduction

This chapter reviews research about the cognitive changes that occur after chemotherapy in children with ALL, intervention strategies to prevent or improve cognitive dysfunction in these children, and risk factors associated with the cognitive changes that occur. Databases including PubMed, CINAHL, and Cochrane were utilized to find appropriate literature, and search terms such as “antineoplastic agents”, “cognition”, and “cognitive interventions” were applied. The criteria for selecting studies were 1) focus on childhood acute lymphoblastic leukemia patients or survivors as a study population 2) research reported between the years of 2007 and 2015. There was no limitation regarding country of publication. A total of 16 studies met the inclusion criteria and will be reviewed in this chapter. Studies that include patients treated with only chemotherapy are discussed first, followed by studies that include patients treated with both chemotherapy and radiation. Intervention studies are then reviewed as well. In each of these sections, studies appear in reverse chronological order.

Studies Including Children Treated Only with Chemotherapy

A 2015 review and meta-analysis by Iyer, Balsamo, Bracken, and Kadan-Lottick assessed long-term neurocognitive functioning among childhood ALL survivors after chemotherapy-only treatment regimens. Ten non-experimental studies were included, all of which were quasi-experimental in design. These studies analyzed neurocognitive outcomes of childhood ALL survivors who met the inclusion criteria of being younger than 21 years at diagnosis, being at least 5 years post-diagnosis or at least 2 years in remission and not receiving treatment, having no history of radiation treatment, being cancer-free at the time of assessment, and comparison with a healthy control group. Results revealed a substantial association between chemotherapy
treatment of childhood ALL and long-term neurocognitive dysfunction. Overall intelligence was most impaired, and there also were significant declines in the areas of working memory, information processing speed, and fine motor skills (Iyer et al., 2015).

Krull, Hockenberry, Miketova, Carey, and Moore (2013) performed a longitudinal study examining the association between cerebrospinal fluid (CSF) phospholipids associated with the integrity of white matter in the brain—such as Sphingomyelin (SM) and lysophosphatidylcholine (LPC)—and neurocognitive outcomes in children undergoing chemotherapy treatment for ALL. Seventy-six children recruited from pediatric hematology/oncology clinics in the Southwestern United States were included in this study, and were followed prospectively from diagnosis. CSF samples were collected during scheduled lumbar punctures to measure phospholipids. Concentrations of SM and LPC were observed at the time of diagnosis, after induction and consolidation chemotherapies, and following the first and second halves of maintenance chemotherapy. Results of this study show that early changes in phospholipids are associated with a decrease in neurocognitive ability and indicate that chemotherapy has a damaging effect on white matter integrity. Specifically, the cognitive areas of motor speed and working memory were significantly affected. Krull et al. (2013) found that early changes in SM correlated with motor speed, early changes in LPC were associated with verbal working memory, and worsening of visual working memory over time was linked to higher SM levels later in therapy.

A randomized controlled trial by Moore, Hockenberry, Anhalt, McCarthy, and Krull (2011) evaluated the effectiveness of a Mathematics Intervention in preventing declines in mathematics abilities among children with newly diagnosed ALL. Fifty-seven children with ALL—32 females and 25 males—in the Southwestern United States were enrolled and randomized to a Mathematics Intervention or standard care. Neurocognitive assessments were
conducted at baseline, at completion of the intervention, and at 1 year after the end of the intervention. Results of this study demonstrate that cognitive stimulation during chemotherapy can prevent deterioration of working memory skills until at least 1 year after conclusion of treatment. Study results showed that the Mathematics Intervention improved mathematics abilities and visual working memory in pediatric ALL patients being treated with chemotherapy when compared to standard care (Moore et al., 2011). The authors suggest that future studies work to translate the Mathematics Intervention into a computer-based technology delivery method in order to make the intervention more accessible to patients and families (Moore et al., 2011).

A comparative study by Jain, Brouwers, Okcu, Cirino, and Krull (2009) evaluated the pattern of attention problems in male versus female long-term childhood ALL survivors. Standardized measures of basic and complex attention skills related to anterior (i.e. inhibition, shifting attention, working memory), posterior (i.e. focusing), and subcortical (i.e. sustaining) brain systems (Jain et al., 2009). The study consisted of 103 long-term survivors. Fifty-one percent of the study participants were male, all were at least 5 years post-diagnosis (average of 7.5 years), and the average age at time of diagnosis was 3.9 years. Jain et al. (2009) found that intensity of treatment was associated with attention, and patients who were high risk and received more intense treatment scored significantly lower. Study results revealed that girls performed worse than boys on measures related to the anterior attention system (i.e. shifting attention) and the subcortical (i.e. sustained attention), and boys performed worse than girls on different measures of anterior control (i.e. inhibition and working memory).

Anderson and Kunin-Batson (2009) systematically reviewed 13 studies to assess the current knowledge of the effects of chemotherapy on children’s brain structure and function as
seen through neuro-cognitive and neuro-imaging studies between the years of 1997 and 2007. The results of this review showed that although chemotherapy is less neurotoxic than radiation, it has significant effects on visual processing, visual-motor functioning, attention, and executive functioning regardless of agent or administration method. Additionally, Anderson and Kunin-Batson (2009) found that girls are affected worse than boys and younger children (under 3 years) experience greater cognitive deficits. It is also concluded that, based on current research, the neurocognitive late effects observed in pediatric ALL survivors treated with chemotherapy are attributable to white matter changes in the brain (Anderson & Kunin-Batson, 2009).

A 2008 study by Lofstad, Reinfjell, Hestad, and Diseth examined cognitive outcomes in children and adolescents whose ALL was in remission and treated only with chemotherapy. This study was experimental in design and included 35 children and adolescents in long-term remission from ALL between the ages of 8.4 and 15.3 years. The participants were anywhere from 4.2-12.4 years post-diagnosis, did not experience relapse, and had no previous history of neurodevelopmental disorders. They were compared with 35 healthy controls matched for gender, age, and socio-demographic variables. Cognitive functioning of both groups was measured using the Wechsler Intelligence Scale for Children—Third Edition (WISC-III). Study results revealed a significant decrease in scores in the areas of attention, processing speed, verbal function, and visual spatial problem solving in the ALL group when compared to the control group (Lofstad et al., 2008).

Buizer, de Sonneville, and Veerman (2008) conducted a systematic review to evaluate current knowledge of the neurocognitive effects of CNS-directed chemotherapy in children with ALL. Twenty-one studies met the inclusion criteria of having a publication date of 1997 or later and including an ALL group treated with chemotherapy and a control group. The studies were
primarily of cross-sectional design, with three studies having a prospective design. Buizer et al. (2008) concluded that childhood ALL survivors encounter long-term neurocognitive deficits after treatment, even without radiation. These deficits are predominantly in the areas of attention and executive functioning, while global intellectual function remains relatively intact (Buizer et al., 2008). Additionally, research revealed that risk factors for developing these cognitive impairments after chemotherapy include young age at diagnosis, female gender, and more intense chemotherapy treatment.

A meta-analysis conducted by Peterson et al. (2008) assessed differences in neuropsychological and academic functioning in children with ALL treated with chemotherapy when compared to a control group that did not receive CNS-directed treatment. Thirteen articles were included from MEDLINE and PsychInfo databases which met the inclusion criteria of: 1) including participants who had completed chemotherapy-only treatment for pediatric ALL and a control group, 2) being written in English, and 3) containing empirical data adequate to calculate effect sizes. Effect size statistics from this review demonstrate a poorer functioning of ALL groups for full scale intelligence quotient (FSIQ), verbal IQ (VIQ), performance IQ (PIQ), math achievement, reading achievement, freedom from distractibility index, perceptual organization index, coding, digital span, Purdue pegboard (both hands), Purdue pegboard (preferred hand), trails B, and verbal memory (Peterson et al., 2008). Additionally, research shows that ALL survivors have difficulty in the academic areas of math and reading. Findings also showed that girls performed worse than boys, indicating that girls may be at greater risk for developing cognitive deficits after chemotherapy treatment for pediatric ALL.

Hockenberry et al. (2007) performed a longitudinal study to investigate fine motor function in children with ALL and motor function that may contribute to neurocognitive deficits
in ALL survivors. Newly diagnosed patients between the ages of 3 and 15 years enrolled in a Pediatric Oncology Group (POG) Protocol no. 9904 (low risk ALL), no. 9905 (standard risk ALL), or no. 9906 (high risk ALL) were eligible for inclusion in this study. Sixty-two patients from Texas Children’s Cancer Center and 20 from the University of Arizona Pediatric Hematology/Oncology were included, for a total of 82 study participants. Evaluations of each patient took place in the outpatient clinic during weekly outpatient appointments, and care was taken to ensure adequate patient effort and motivation on each test. Results showed that visual motor integration problems were not evident at baseline, but a significant decline in performance was present at 1- and 2-year follow-ups. This decline in visual motor integration was predicted by the baseline performance on the Purdue Pegboard test, which suggests that early reductions in fine motor speed lead to reduced visual motor integration (Hockenberry et al., 2007).

Hockenberry et al. (2007) propose that early declines in fine motor speed are likely due toxicity of chemotherapy agents (including vincristine and methotrexate.) Additionally, no significant difference in results between ALL risk groups was found, despite the fact that intensity of chemotherapy treatment increases with risk classification (Hockenberry et al., 2007).

**Studies Including Children Treated with Chemotherapy and Radiation**

Castellino, Ullrich, Whelen, and Lange (2014) conducted a systematic review to assess the relationship between current cancer treatment and the epidemiology and pathophysiology of cognitive dysfunction. The authors used the results from the review to develop pharmacologic and non-pharmacologic interventions for cancer-related cognitive dysfunction in childhood cancer survivors. Pediatric cancers addressed include brain tumors, ALL, and tumors involving the head and neck. A total of 257 studies from PubMed were included after meeting the inclusion criteria of being written in English and published between 1990 and December 2012.
Castellino et al. (2014) found that risk factors for cancer-related cognitive impairment include young age at time of diagnosis, use of radiation, treatment with parenteral or intrathecal methotrexate, female gender, polymorphisms in the MTHFR gene, and presence of pre-existing comorbidities. Limiting use and decreasing doses of radiation while intensifying chemotherapy treatment regimens have reduced occurrence of cognitive dysfunction, especially in leukemia patients (Castellino et al., 2014). However, results of this review also reveal that problems in fundamental functional domains of attention, processing speed, working memory, and visual-motor integration remain an issue. The authors proposed educational and behavioral interventions for both prevention and alleviation of already established cognitive dysfunction.

Prevention strategies, implemented at the time of diagnosis and during treatment, include pharmacological interventions such as anti-inflammatory agents, nutrition, and stimulant drugs. Interventions aimed at symptom alleviation and prevention of further cognitive decline, implemented after treatment has ended, include pharmacological interventions such as stimulant drugs, donepezil, modafinil, and growth hormone replacement. Behavioral strategies that have shown to be beneficial both in prevention and alleviation of cognitive dysfunction include educational interventions, cognitive remediation, and cardiovascular exercise. (Castellino et al., 2014).

A systematic review by Moore, Hockenberry, and Krull (2013) explored the cognitive changes associated with CNS-directed chemotherapy and radiation which are experienced by children with cancer and adult survivors of childhood cancer. The two types of cancer that are discussed in this review are ALL and brain tumors, because they are the two most common types of childhood malignancies (Moore et al., 2013). Interventions for the prevention or remediation of cognitive and academic difficulties related to CNS-directed cancer treatment are also
summarized in this review. Results revealed that with high doses of radiation, impairment is frequently seen in global cognitive abilities, such as intelligence and academic functions (Moore et al., 2013). When treatment consists of lower doses of radiation and high-dose chemotherapy, impairment is more often seen in the specific cognitive abilities of attention, processing speed, and executive functions such as fluency, cognitive flexibility, and working memory (Moore et al., 2013). Interventions aimed at improving cognitive and academic outcomes associated with CNS-directed cancer treatment discovered by Moore et al. (2013) in this review include a stimulant medication called methylphenidate (MPH) and cognitive and/or problem solving interventions. Patients taking MPH had a serious reaction to the medication, so its potential benefits are outweighed by its toxic nature. However, cognitive and problem solving interventions were effective in improving aspects of cognitive and academic functioning. These interventions include a mathematics intervention, a computerized cognitive training program, a teaching compensatory learning and problem-solving skills intervention, and a cognitive remediation program (CRP). The mathematics intervention by Moore et al. (2011) was discussed previously in this chapter. The computerized cognitive training program studied by Hardy et al. (2011) was found to improve digit-span forward (a measure of working memory) and decrease parents’ report of cognitive problems in their children. Patel et al. (2009) tested a teaching compensatory learning and problem-solving skills intervention resulting in significant improvement in academic performance—specifically writing skills—and an aspect of social skills. The CRP tested by Butler et al. (2008) improved academic function and attention. These studies will be discussed individually in more detail throughout the rest of this chapter.

Hardy, Willard, and Bonner (2011) conducted a pilot study to test the efficacy of a computerized cognitive training program, *Captain’s Log*, in a total of nine childhood ALL and
brain tumor survivors with recognized attention and working memory impairment. Participants were from pediatric hematology/oncology and neuro-oncology divisions of a medical center in the Southeastern United States, they were between the ages of 10 and 17 years, and were at least 1 year post-treatment. The training program was home-based and lasted 12 weeks, consisting of 33 engaging “brain-training” exercises intended to improve processing speed, memory, attention, concentration, self-control, listening skills, and patience (Hardy et al., 2011). Three months following the intervention, participants were re-evaluated and demonstrated a significant increase in working memory with a decrease in parent-rated attention problems (Hardy et al., 2011). While the findings of this study are promising, the authors state that further studies with larger samples are needed.

A pilot study by Patel, Katz, Richardson, Rimmer, and Kilian, (2009) tested a teaching compensatory learning and problem-solving skills intervention with pediatric cancer survivors treated with cranial radiation and/or chemotherapy. The intervention was a clinic-based training program consisting of 15 sessions aimed at improving attention and memory, daily problem solving, and overall academic performance (Patel et al., 2009). Twelve children completed the intervention—nine of which were diagnosed with brain tumors, two with leukemia, and one with CNS-involved histiocytosis. Participants were evaluated pre- and post-intervention, and displayed significant improvement in writing and social skills after completion of the program (Patel et al., 2009). Although the results are favorable and the majority of enrolled families completed at least 70% of the total training sessions, the overall low participation rate from families suggests that programs like this one may not be well-accepted in the oncology clinic (Patel et al., 2009).
An experimental study by Harila, Winqvist, Lanning, Bloigu, and Harila-Saari (2009) evaluated neuropsychological functioning in a population of 64 young adult childhood ALL survivors treated at the Oulu University Hospital from 1971-1994 who were at least 18 years old. Participants had to have been diagnosed at least 10 years earlier, have no evidence of leukemia at the time of the evaluation, and be living in Finland (Harila et al., 2009). Four different groups of tests were used to evaluate participants: tests that assessed intellectual functions, memory functions, orientation and attention, and motor performance. Results showed that survivors treated with cranial radiation displayed apparent deficits in neurocognitive functioning at an average of 20 years after diagnosis when compared to healthy controls (Harila et al., 2009). These survivors scored significantly lower in areas of verbal and performance IQ, memory functions, orientation and attention, and motor functions (Harila et al., 2009). Survivors not treated with cranial radiation performed better that those treated with cranial radiation, but their scores were still significantly lower than the control group in the areas of verbal and performance IQ, sequential reasoning, working memory, and information processing speed (Harila et al., 2009).

Butler et al. (2008) conducted a study to evaluate a randomized clinical trial of the Cognitive Remediation Program (CRP). The CRP combines interventions from three different approaches: brain injury rehabilitation, child clinical psychology, and educational psychology (Butler et al., 2008). One hundred sixty-one childhood cancer survivors between the ages of 6 and 17 years who were at least 1 year post-treatment and who demonstrated an attention deficit were included in this study. Childhood malignancies represented in this study include leukemia, brain tumors, non-Hodgkin’s lymphoma, and bone marrow transplants involving total body radiation (Butler et al., 2008). Two-thirds of the participants were randomly assigned to the
CRP, and all participants were assessed using a series of academic achievement/neurocognitive tests and parent/teacher measures of attention (Butler et al., 2008). The CRP resulted in enhanced attention reported by parents and significant improvements in academic performance (Butler et al., 2008). While the improvements were statistically significant, the effect sizes were relatively small. However, the effect sizes in this study were similar to those of previous clinical trials for brain injury rehabilitation and for psychological interventions overall (Butler et al., 2008).

**Conclusion**

The articles reviewed in this chapter addressed cognitive deficits experienced by childhood cancer survivors and the efficacy of interventions aimed at preventing and improving these deficits. The studies varied in design from systematic reviews to clinical trials and included both large and small sample sizes. The reviewed studies consistently indicated that chemotherapy treatment of childhood ALL causes long-term cognitive impairment, specifically in the areas of total IQ, attention, processing speed, visual memory, working memory, problem solving, sequential reasoning, and academic achievement in math and reading. Research results identified chemotherapy’s effect on the integrity of white brain matter as the source of these neurocognitive impairments. Additionally, interventions discussed that were shown to be beneficial in improving cognitive outcomes were cognitive and problem solving interventions. See Table 1 in Appendix A for a summary of the information gathered from these articles. Based on this review of literature, an educational intervention is necessary among the population of children undergoing treatment for ALL, even in the absence of radiation, as well as survivors of pediatric ALL.
CHAPTER 3: PROPOSED BEST PRACTICE PROTOCOL

Introduction

The purpose of this thesis is to create an evidence-based educational pamphlet to inform parents and help facilitate the learning experience of children during and after treatment for ALL. The primary focus is on chemotherapy treatment of ALL because radiation is only used to treat children with high- or very high risk disease (Castellino, Ullrich, Whelen, & Lange, 2014). This chapter will detail the proposed best practice recommendations to help nurses and other medical personnel provide parents of children undergoing treatment for ALL with important information that will help them be proactive in promoting their child’s cognitive function and quality of life after treatment.

The literature reviewed in the previous chapter presented important information regarding chemotherapy and its effect on the developing brain, as well as interventions that were shown to be successful in improving and/or preventing cognitive deficits during and after chemotherapy in pediatric ALL patients. Studies show that chemotherapy alters the integrity of white matter in the brain (Krull et al., 2013), which connects the different regions of gray brain matter and is responsible for transmission of electrical signals between different brain regions (Fields, 2011). White brain matter is thought to be more susceptible to damage in children because the newly produced myelin has a higher metabolic rate and is less stable (Anderson & Kunin-Batson, 2009).

The cognitive areas in which deficits are primarily noted in children treated with chemotherapy for ALL are attention, working memory, information processing speed, motor speed, problem solving, and sequential reasoning (Anderson & Kunin-Batson, 2009; Duffner et al., 2014; Harila et al., 2009; Iyer et al., 2015; Lofstad et al., 2009; Peterson et al., 2008). Risk
factors for the development of cognitive problems include age at diagnosis, gender, and existence of comorbidities. While ALL is statistically more common in boys, research shows that girls have worse cognitive outcomes following chemotherapy treatment (Anderson & Kunin-Batson, 2009). Additionally, children who are younger at the time of diagnosis have greater deficits (Anderson & Kunin-Batson, 2009). Pre-existing comorbidities also increase the child’s risk of experiencing post-chemotherapy cognitive deficits (Castellino, Ullrich, Whelen, & Lange, 2014).

**Education as a Primary Intervention**

An evidence-based educational tool can serve as a primary intervention to inform parents of ways to combat the cognitive effects that may occur as a result of chemotherapy, as well as provide information to help parents effectively advocate for their child as he/she returns to school after treatment. The goal is to optimize children’s academic performance and quality of life after cancer, which is not possible without active parent involvement. It is important that parents are educated so that they can provide the necessary enriched environment, can be aware of certain warning signs, and can effectively advocate for their child to maximize their child’s quality of life after cancer. See the proposed evidence-based educational pamphlet in Appendix C.

**Summary of Proposed Educational Pamphlet**

The proposed evidence-based educational pamphlet will include the most relevant and most important information for parents of children diagnosed with ALL. This pamphlet will contain information regarding the disease process of ALL, current treatments, early and late effects of treatment, risk factors for experiencing treatment-related cognitive problems, and interventions to help prevent and improve cognitive deficits. See Table 2 for the proposed best
practice protocol regarding content inclusion of the educational pamphlet. The primary objective of this pamphlet is to provide parents of children diagnosed with ALL with thorough and comprehensible evidence-based information so they can be proactive in preserving their child’s cognitive function and promoting their education. With this knowledge, parents can take the appropriate steps to ensure the best cognitive outcomes possible in order for their child to maintain a good quality of life after treatment. This pamphlet will specifically be implemented within the setting of pediatric oncology outpatient clinics where children are diagnosed with ALL and treatment plans are discussed. Additionally, this pamphlet will be readily available in waiting areas of cancer centers and outpatient clinics for the information of families and visitors.
Table 2

Best Practice Protocol

<table>
<thead>
<tr>
<th>Content of Pamphlet</th>
<th>Topics</th>
<th>References</th>
</tr>
</thead>
</table>
| What is ALL         | - ALL is a cancer of the blood and bone marrow and is the most common pediatric malignancy  
- Accounts for 25% of cancers in children under 15 years of age and 19% of cancers in those younger than 20 years of age | Hunger et al., 2012 |
| Common treatments for ALL | - Chemotherapy  
- Radiation  
- Bone Marrow Transplantation | Hunger & Mullighan, 2015; Ward et al., 2014 |
| Effects of treatment | - Early effects  
- Late effects | Leukemia & Lymphoma Society, 2013 |
| Cognitive Problems | - Thinking  
- Memory  
- Learning | Anderson & Kunin-Batson, 2009; Duffner et al., 2014; Harila et al., 2009; Iyer et al., 2015; Lofstad et al., 2009; Peterson et al., 2008 |
| Risk Factors | - Who is at greatest risk for experiencing cognitive decline during and after treatment? | Anderson & Kunin-Batson, 2009; Castellino, Ullrich, Whelen, & Lange, 2014 |
| Improvement and Prevention | - Cognitive and problem-solving interventions  
- Computerized cognitive training  
- Early psychological family therapy  
- Advocating for your child’s education | Butler et al., 2008; Moore, Hockenberry, & Krull, 2013; Patel et al., 2009; Hardy et al., 2010; Moore et al., 2012 |
CHAPTER 4: IMPLEMENTATION AND EVALUATION

Introduction

This chapter will focus on implementing an educational pamphlet about the cognitive problems that occur in children undergoing ALL treatment. Nurses and other health care professionals can utilize this pamphlet to provide parents of children being treated for ALL with comprehensive information about the cognitive problems that commonly occur with current treatment regimens, as well as associated risk factors and ways to prevent and improve these complications. The steady increase in childhood ALL survival rates is associated with an increased occurrence of cognitive deficits related to ALL treatment. As of 2013, the rate of occurrence of cognitive deficits in childhood ALL survivors who received chemotherapy and/or radiation is up to 40% (Moore, Hockenberry, & Krull, 2013). Many parents are uninformed about these potential complications, preventing them from seeking the appropriate help or making the necessary interventions to ensure their child’s academic success and optimal quality of life after cancer. By implementing the use of an educational pamphlet in medical institutions where children with ALL are treated, more parents will be educated about potential cognitive challenges during/following their child’s treatment. This will empower parents to intervene and advocate for their child accordingly.

In order to implement this intervention, research regarding effective design and content style of educational brochures/pamphlets and Rogers’ (2003) theory of Diffusion of Innovations will be applied. The educational pamphlet will incorporate techniques that facilitate effective translation of important information to a target audience. Formatting and simplifying the information gathered from the literature review will be the major focus in developing an educational pamphlet. The Diffusion of Innovations theory will serve as a guide for the
introduction and implementation of applicable information in the setting of pediatric oncology clinics. The theory of Diffusion of Innovations is a commonly used social theory that guides and promotes the successful implementation of evidence-based research into clinical practice (Rogers, 2003). It consists of five stages: knowledge, persuasion, decision, implementation, and confirmation (Rogers, 2003). Knowledge, persuasion, decision, and implementation are the stages relevant to the implementation process, and will be addressed in the first portion of this chapter. The confirmation stage of the Diffusion of Innovations theory will be used to illustrate the evaluation process of the pamphlet.

**Implementation and Evaluation**

**Creating an Effective Pamphlet**

For children battling ALL and their parents, returning to school inspires hope for the future (Leukemia and Lymphoma Society, 2013). However, with families’ main focus on getting through treatment for such a long period of time, going back to school presents new challenges to them. These challenges include the child’s acceptance and perception by peers related to the short-term, outward signs of the illness (i.e. hair loss), as well as potentially long-term late effects of the cancer treatment (i.e. cognitive deficits). By educating parents about these possible obstacles, they can be better prepared to help their child overcome the challenges. Distribution of an educational pamphlet in pediatric oncology clinics is one method that can be used to effectively deliver evidence-based information to this particular population.

When developing a pamphlet, simplicity of the presented information, as well as the format and color scheme, must be addressed (Pennisi, Gunawan, Major & Winder, 2011). The U.S. Department of Health and Human Services’ Centers for Disease Control and Prevention (CDC) states that health literacy—or an individual’s ability to obtain and understand basic
healthcare-related information or services—impacts a person’s ability to retain information or grasp the meaning of a particular healthcare-related document (CDC, 2015). The content of a pamphlet is a crucial determinant of whether or not the target audience retains the desired information. When selecting information to include in an educational pamphlet, it is important to assess the simplicity of the language used (Pennisi et al., 2011). Translating the information to a third grade reading level will enable individuals with a basic level of health literacy to obtain the necessary education about cognitive late effects of ALL treatment in children (CDC, 2015). Additionally, keeping the content of the pamphlet concise will facilitate readers’ engagement in the material and ensure that they have the pamphlet in their possession for the longest period of time possible to absorb the maximum amount of information (Pennisi et al., 2011).

The Lexile Analyzer, produced by MetaMetrics, was used to evaluate the reading grade level of the evidence-based educational pamphlet. This software tests the readability of uploaded documents by calculating a Lexile measure, which measures sentence length and word familiarity (CDC, 2009). The Lexile measure scale ranges from lower than 200L for beginner-level reading material to over 1700L for advanced texts (CDC, 2009). When a document is uploaded to the Lexile Analyzer, it is compared to a large database of literature. The estimated Lexile score of the evidence-based educational pamphlet is 1130L (MetaMetrics, 2016). According to the Common Core State Standards (CCSS) for English Language Arts (2012) this estimated Lexile score corresponds with the eighth grade reading level and higher (MetaMetrics, 2016). See Appendix B for the Lexile-to-Grade Correspondence Chart. The goal was for the pamphlet to correspond to a third grade reading level to follow the CDC health literacy recommendation. This goal was not met. However, the Lexile Analyzer does not take into
account the use of medical terminology (i.e. “Acute Lymphoblastic Leukemia” and “chemotherapy”) and subsequent explanation of this terminology in simpler terms.

The layout of the pamphlet should be attractive and well organized (Pennisi et al., 2011). The front panel should clearly state the pamphlet’s educational purpose and give the reader an understanding of what they should expect to learn from the pamphlet (Pennisi et al., 2011). On the inside of the pamphlet, bullet points, text boxes, and images help organize the information while establishing style and flow (Pennisi et al., 2011). Additionally, the font size should be easy to read. When choosing the pamphlet’s design and color scheme, it is important to consider the target audience (Pennisi et al., 2011). For parents of children with cancer, a bright, cheery color scheme will be applied to make the content appear inviting, positive, and hopeful.

Once the pamphlet is created using Microsoft Word, its content will be evaluated before mass production and implementation. Small focus groups (five participants per focus group) of willing parents and professionals will perform these evaluations. Parents will evaluate the pamphlet’s readability and professionals will evaluate the pamphlet’s content for accuracy.

**Theory of Diffusion of Innovations**

The theory of Diffusion of Innovations will be utilized in the theoretical implementation of this evidence-based best practice project. This theory was established by Everett M. Rogers and is commonly used in the clinical setting to implement and evaluate evidence-based practice (Rogers, 2003). The five stages in the Diffusion of Innovations theory will be discussed: knowledge, persuasion, decision, implementation, and confirmation (Rogers, 2003). This evidence-based educational pamphlet will be theoretically implemented in a pediatric oncology clinic in the Southwestern United States.
Knowledge. Knowledge is the first stage of the theory of Diffusion of Innovations. This stage begins when the pediatric oncology clinic staff are exposed to the educational pamphlet and understand its purpose and function (Rogers, 2003). Clinic educators will need to acknowledge the increasing number of childhood ALL survivors that are experiencing cognitive problems and the correlation between these late effects and the treatment the children received. The educators will then likely attribute the lack of preventative measures taken by parents to a lack of knowledge about the cognitive problems that commonly occur, as well as available interventions to prevent and improve these problems. Most importantly, the educators at the pediatric oncology clinic must recognize the need for education and the importance of providing an educational resource to parents of children undergoing treatment for ALL.

Clinic educators must be aware of the prevalence of cognitive problems in childhood ALL survivors in order to be able to recognize the need for education. Ways in which this knowledge can be obtained include follow-up appointments, professional medical and nursing journals, and a short presentation at a staff meeting regarding the evidence in support of educating parents about treatment-related cognitive problems and effective interventions. At follow-up appointments with patients and families, providers will learn of cognitive problems that children may be experiencing. Over time they may recognize the trend and relay this information to clinic educators. Professional medical and nursing journals have the potential to feature articles that address the cognitive late effects that occur in pediatric ALL patients and survivors, as well as the related risk factors and feasible interventions. A short presentation at a staff meeting will quickly bring the issue to providers’ attention. The exposure to knowledge about cognitive problems in childhood ALL patients and survivors can prompt educators to recognize the need for an educational intervention of some kind. Once a need to intervene has
been identified, the implementation process can progress to the persuasion stage of implementation (Rogers, 2003).

**Persuasion.** The persuasion stage of the Diffusion of Innovations theory states that the clinic educators will cultivate either a positive or negative view of the intervention to educate parents about cognitive problems that commonly occur in children treated for ALL after attending an informational meeting and reading relevant articles in a professional medical/nursing journal (Rogers, 2003). The expected outcome is that the educators will develop a positive view of the intervention, demonstrating their development of a sense that parents of children with ALL need to be educated about possible cognitive late effects, associated risk factors, and effective interventions to prevent and remediate the cognitive problems. Educators will take the newly gained knowledge about this issue and move forward with the intent to modify parents’ actions (Rogers, 2003). They will do so by implementing an evidence-based educational intervention.

**Decision.** In the decision-making stage of the Diffusion of Innovations theory, an individual or organization makes the decision to either implement or reject a proposed innovation (Rogers, 2003). The pediatric oncology clinic’s administrative board will determine that incorporating education regarding cognitive problems in children treated with chemotherapy and radiation for ALL into treatment teaching is a realistic and beneficial intervention. The cost of producing the pamphlet would need to be considered, as well as the cost of educating doctors and nurses of the evidence-based information to be presented to parents. This particular intervention could be carried out in monthly staff meetings, eliminating additional costs of employee education. As a result, implementation of this intervention would be inexpensive and relatively straightforward.
Implementation. In the implementation stage of the Diffusion of Innovations theory, nurses and providers would begin using the educational pamphlet in patient and family teaching (Rogers, 2003). This requires a change in behavior, as the healthcare providers would need to ensure the inclusion of information regarding potential cognitive late effects of chemotherapy and radiation treatment regimens for ALL in patient and family teaching sessions (Rogers, 2003). While employee education would occur in at least one meeting prior to implementing the pamphlet into practice, additional educational meetings about the educational pamphlet and how to best present the material to patients and families will be held periodically as needed.

Confirmation. As the final stage of the Diffusion of Innovations theory, the confirmation stage serves as a means of evaluating the efficacy of the proposed best practice intervention. During this stage, clinic board members will evaluate the usefulness of implementing the educational pamphlet in patient and family teaching sessions (Rogers, 2003). At this point, the healthcare professionals will have received the necessary education to effectively teach patients and families about cognitive problems that can occur in children being treated for ALL with chemotherapy and/or radiation, and should be utilizing the educational pamphlet in teaching sessions. There are two aspects of the implementation process that will be evaluated: 1) whether or not health care providers are teaching parents about cognitive late effects that can occur in children treated for ALL, and 2) whether or not the teaching was valuable to the parents who received it.

Healthcare providers’ teaching efficacy. After three months of implementing the educational pamphlet, individuals on the pediatric oncology clinic’s board of directors will distribute mandatory questionnaires to all healthcare professionals who have provided education to children with ALL and their families. The questionnaire will be sent online via electronic
mail (e-mail), making it easy for individuals to quickly complete the questionnaire and return it. This will produce a more comprehensive evaluation of the intervention’s efficacy, as individuals will be more likely to respond to an e-mail versus a postal mail questionnaire.

The content of individual healthcare providers’ patient and family teaching sessions is largely individualized based on what he/she perceives to be important information. They have the ability to determine what aspects of the overall education about the disease process and treatment are addressed during each teaching session. In order to thoroughly evaluate the educational pamphlet’s efficacy, it is important to know whether educators are recognizing a demand for education regarding cognitive late effects. The electronic questionnaire would confirm the knowledge and persuasion stages of the Diffusion of Innovations theory by determining whether the doctors and nurses understand the value in educating parents about cognitive late effects in children treated for ALL (Rogers, 2003). It would also confirm their decision to utilize the educational pamphlet in patient and family teaching (Rogers, 2003).

Confirmation of parental education. In order to confirm the implementation of the evidence-based educational pamphlet, it will be necessary to obtain feedback from parents about their experience with the pamphlet. Feedback regarding whether they found the information to be beneficial and whether it influenced them to seek early intervention to prevent cognitive deficits in their child is essential in evaluating the pamphlet’s efficacy. The parents will be asked to complete a questionnaire at their child’s next visit, giving them the opportunity to provide their opinion of the pamphlet’s readability and whether or not they found the information to be meaningful. Parents will also have the opportunity to list any aspects or details of the pamphlet that they would have preferred to be excluded, included, or altered. There will also be space for parents to ask any remaining questions that they may have about this important topic.
The intended outcome for the implementation of the educational pamphlet is that parents will gain important knowledge about the cognitive effects of chemotherapy and radiation in children with ALL, including specific risk factors and intervention strategies. This knowledge will empower parents to advocate for their child, and take the appropriate steps to prevent cognitive deficits and ensure the best quality of life possible for their child after cancer. The confirmation stage will confirm that parents are adequately educated about the cognitive deficits that occur in children treated for ALL, as well as the associated risk factors and ways to prevent and improve these deficits. The confirmation stage will also determine whether or not the pamphlet was user-friendly and if parents benefited from its use.

Summary

The process for implementation of the evidence-based educational pamphlet was developed using research about elements of an effective pamphlet and Rogers’ theory of Diffusion of Innovations. Creating an effective pamphlet ensures that the information regarding cognitive deficits seen in children treated for ALL is meaningfully received by parents. Diffusion of Innovations is a social theory that outlines the steps necessary to successfully implement and evaluate evidence-based practice into a healthcare setting (Rogers, 2003). The five steps of the Theory of Diffusion of Innovations are knowledge, persuasion, decision, implementation, and confirmation (Rogers, 2003).

Conclusion

The purpose of this thesis was to summarize current knowledge about the neurocognitive changes associated with chemotherapy treatment in children with ALL, as well as associated risk factors and intervention strategies. This information was compiled into an evidence-based educational pamphlet, with the goal of increasing awareness of cognitive changes that occur with
chemotherapy in pediatric ALL patients and educate about evidence-based intervention strategies to help prevent or remediate these cognitive changes. Research results revealed that children with ALL treated with chemotherapy have neurocognitive impairment in the areas of total IQ, working memory, attention, information processing speed, fine motor speed, visual IQ, verbal IQ, performance IQ, problem solving, and sequential reasoning. Affected children also perform poorly in the academic areas of mathematics and reading (Peterson et al., 2008). Research indicates that interventions that are effective in improving cognitive outcomes include cognitive and/or problem-solving interventions (Moore, Hockenberry, & Krull, 2013). Risk factors for experiencing ALL treatment-related cognitive dysfunction include young age at diagnosis, female gender, and existence of comorbidities. Overall, the implementation of this best-practice educational pamphlet will serve to educate and empower parents to advocate for their children, as well as promote their academic performance and quality of life after cancer.
References


### Table 1: Table of Evidence

<table>
<thead>
<tr>
<th>Author(s) and Date</th>
<th>Objectives, Hypothesis</th>
<th>Design, Sample</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Iyer, Balsamo, Bracken, & Kadan-Lottick, 2015 | • Objective: to assess the long-term neurocognitive functioning of childhood ALL survivors who received chemotherapy (chemo) treatment regimens. | • Meta-Analysis and Review  
• 10 non-experimental studies | • Statistically significant moderate impairment across multiple neurocognitive domains evaluated, with intelligence most affected  
• Significant differences in standard deviation (SD) scores found for full scale intelligence quotient (IQ), verbal IQ (VIQ), and performance IQ (PIQ)  
• Working memory, information processing speed, and fine motor domains were moderately, but statistically significantly, impaired |
| Castellino, Ullrich, Whelen, & Lange, 2014 | • Objective: to review the impact of modern cancer treatment on the epidemiology and pathophysiology of cognitive dysfunction, while exploring targeted neurocognitive assessments as a way to monitor outcomes.  
• This study also describes pharmacologic and non-pharmacologic interventions to improve established cognitive dysfunction | • Systematic Review  
• 257 studies selected from PubMed | • Cognitive remediation program improved academic performance  
• School-based math intervention improved math skills and visual working memory in the intervention group vs. decline in control group  
• Computerized training program improved working memory and attention  
• Cogmed RM improved visual working memory and decreased prevalence of learning problems  
• Social skills intervention resulted in higher perceived classmate and teacher social support and decreased internalizing/externalizing behaviors in newly diagnosed pediatric cancer patients  
• Psychological intervention reduced anxiety and parental PTSD symptoms with newly diagnosed pediatric cancer patients  
• Ongoing cancer therapy trials to reduce neurotoxicity of treatment by modifying CrRT and chemotherapy to develop less toxic, more individualized therapy |
| Duffner et al., 2014 | • Objective: to determine whether there are differences in the neurocognitive function and neuroradiologic findings of leukoencephalopathy in children treated on P9605 versus P9201 treatment regimens | • Comparative study  
• 66 children from 16 Pediatric Oncology Group institutions with “standard-risk” ALL, 1.00-9.99 years at diagnosis, and without evidence of CNS leukemia at diagnosis were enrolled on ACCL0131: 28 from P9201 and 38 from P9605. | • Significantly more patients treated with P9605 had leukoencephalopathy and white matter changes on MRI than those treated with P9201  
• Strong relationship identified between MRI evidence of leukoencephalopathy and neurocognitive function  
• Neurocognitive late effects related to ALL have been consistently identified in areas of attention, distractibility, speed of information processing, verbal memory, visual memory, verbal comprehension, visuospatial skills, visuo-motor integration, and executive function |
<table>
<thead>
<tr>
<th>Author</th>
<th>Objective</th>
<th>Study Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis, Perry, &amp; Murdoch, 2013</td>
<td>Objective: to examine language skills of 9 children following intrathecal chemotherapy (ITC) for ALL and 9 age- and sex-matched controls at baseline, then again 2 years later using tests to assess general language skills. Hypothesis: ALL survivors will display a deficit in language performance over a 2-year period when compared to control.</td>
<td>Quasi-Experimental</td>
<td>ALL survivors showed no notable difference in language performance over a 2-year period when compared to control group</td>
</tr>
<tr>
<td>Krull, Hockenberry, Miketova, Carey, &amp; Moore, 2013</td>
<td>Objective: to examine the association between CSF phospholipids associated with white matter integrity and neurocognitive outcomes in children undergoing chemo treatment for ALL.</td>
<td>Longitudinal Study</td>
<td>Early changes in phospholipids are related to neurocognitive decline and suggest a chemotherapy impact on white matter integrity. A previous study by Krull et al. found that cognitive stimulation during active chemo can prevent declines in working memory skills; results from this study reinforce those findings.</td>
</tr>
<tr>
<td>Anderson &amp; Kunin-Batson, 2009</td>
<td>Objective: to review what has been discovered about the effects of chemo on children’s brain structure and function as seen through neuro-imaging and neuro-cognitive studies over the past 10 years and discuss future directions.</td>
<td>Systematic Review</td>
<td>Chemo alone is less neurotoxic than radiation, but does have effects on specific neuro-cognitive functions such as visual processing, visual-motor functioning, attention, and executive functioning. Neuro-cognitive late effects attributable to changes in white matter. Girls are affected worse than boys. Younger children (&lt;3 years) have greater deficits.</td>
</tr>
<tr>
<td>Lofstad, Reinfjell, Hestad, &amp; Diseth, 2008</td>
<td>Objective: to examine cognitive outcome in children and adolescents with acute lymphoblastic leukemia (ALL) in remission, treated with central nervous system prophylactic chemo. Hypothesis: early childhood ALL treated by chemo only influences subsequent brain development and is followed by cognitive sequelae.</td>
<td>Experimental</td>
<td>All but 2 ALL survivors treated with chemo obtained WISC-III Total Intelligence Quotient (IQ) scores in the normal range, but their scores were significantly below those of the controls and below normative standards. Significant difference between patients and controls for total IQ, VIQ, verbal comprehension, freedom from distraction index, and three verbal subtest scores. Results indicate long-term sequelae in global cognitive functions, and indicate that verbal function, processing speed, attention, and complex visual-spatial problem solving may be affected in the chemo only group.</td>
</tr>
<tr>
<td>Jain, Brouwers, Okcu, Cirino, &amp; Krull, 2009</td>
<td>Objective: to evaluate the pattern of attention problems in male and female long-term survivors of pediatric ALL. Hypothesis: girls are more likely to exhibit impairment related to subcortical brain systems due to their lower gray to white matter volume compared to boys’.</td>
<td>Experimental; Comparative Study</td>
<td>Treatment intensity was related to sustained attention, with patients treated on high-risk protocols displaying significantly lower performance. Girls performed worse than boys on measures related to anterior attention system (i.e. shifting attention) and the subcortical (i.e. sustained attention). Boys performed worse than girls on different measures of anterior control (i.e. inhibition; working memory).</td>
</tr>
<tr>
<td>Patel, Katz, Richardson, Rimmer, &amp; Kilian, 2009</td>
<td>Objective: to evaluate participants’ acceptance and impact of a 15-session, clinic-based training program to teach compensatory learning and problem-solving skills in survivors with cognitive deficits.</td>
<td>Pilot Study</td>
<td>Although the majority of enrolled families completed at least 70% of the training sessions, the overall low participation rate from families raises concern about the acceptance of programs like this one in oncology clinics.</td>
</tr>
<tr>
<td>Reference</td>
<td>Objective</td>
<td>Methodology</td>
<td>Findings/Directions</td>
</tr>
<tr>
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<tr>
<td>Harila, Winqvist, Lanning, Bloigu, &amp; Harila-Saari, 2009</td>
<td>Objective: to assess neuropsychological functioning in a population-based cohort of young adult childhood ALL survivors</td>
<td>Experimental</td>
<td>64 young adult survivors of ALL treated at the Oulu University Hospital 1971-1994 who were at least 18 years old within 6 months of the invitation, and who had been diagnosed at least 10 years earlier, had no evidence of leukemia at the time of the evaluation, and were living in Finland.</td>
</tr>
<tr>
<td>Buizer, de Sonneville, &amp; Veerman, 2008</td>
<td>Objective: to assess what is known of the neuro-cognitive effects of CNS-directed chemo in children with ALL, and to formulate directions for future research.</td>
<td>Systematic Review</td>
<td>21 studies published since 1997 that include an ALL group treated with chemo and a control group</td>
</tr>
<tr>
<td>Peterson et al., 2008</td>
<td>Objective: to conduct a meta-analysis assessing neuropsychological and academic functioning differences between children with ALL treated solely with chemotherapy and comparison groups</td>
<td>Meta-Analysis</td>
<td>13 articles included from MEDLINE and PsychInfo databases</td>
</tr>
<tr>
<td>Janzen &amp; Spiegler, 2008</td>
<td>Objective: to describe the neurocognitive outcomes associated with pediatric ALL and treatment, and to address methodical issues, treatment factors, risks, social populations, relationship to neuroimaging findings, and directions for future research</td>
<td>Systematic Review</td>
<td>Unknown volume of studies reviewed</td>
</tr>
<tr>
<td>Hockenberry et al., 2007</td>
<td>Objective: to investigate fine motor function in children with ALL and motor function that may contribute to neurocognitive deficits in ALL survivors</td>
<td>Longitudinal Study</td>
<td>82 children with ALL; 62 from Texas Children’s Cancer Center and 20 from the University of Arizona Pediatric Hematology/Oncology</td>
</tr>
<tr>
<td>Moore, Hockenberry, Anhalt, McCarthy, &amp; Krull, 2012</td>
<td>Objective: The aim of the study was to determine if the Mathematics Intervention was effective in preventing declines in mathematics abilities among children with newly diagnosed ALL.</td>
<td>Randomized Controlled Trial</td>
<td>57 children were randomized to either the Mathematics Intervention or the Standard Care Group during the continuation phase of chemotherapy for childhood ALL.</td>
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<tr>
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<td>Survivors of childhood ALL suffer from long-lasting progressive neuropsychological impairment, especially when treatment includes radiation.</td>
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<td>Young adult survivors of childhood ALL treated with cranial irradiation had clear progressive deficits in neurocognitive functioning compared to healthy controls</td>
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<td>Non-radiated ALL survivors performed significantly better than radiated survivors, but they still had statistically significant impairments in some neuropsychological test scores compared to the controls, particularly in the areas of VIQ and PIQ, sequential reasoning, working memory, and processing speed.</td>
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<td>Childhood ALL survivors experience subtle long-term neurocognitive deficits after treatment, even in the absence of radiation.</td>
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<td>Effect size statistics show poorer functioning of ALL groups for FSIQ, VIQ, PIQ, math and reading achievement, freedom from distractibility index, perceptual organization index, coding, digital span, Purdue pegboard (both hands), Purdue pegboard (preferred hand), trails B, and verbal memory.</td>
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<tr>
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<td>Girls may be at greater risk than boys for having decreased neuropsychological and academic functioning</td>
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<td></td>
<td>Neurocognitive outcome for the majority of children with standard-risk ALL treated according to current chemo protocols is relatively good, but subgroups of children are more significantly compromised.</td>
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<td></td>
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<td></td>
<td>Poorer intellectual outcomes are found for girls and children who are younger at diagnosis</td>
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<td></td>
<td>Visual motor integration problems were not apparent at Baseline, but a significant decline in performance was evident at year 1 and year 2 follow-up</td>
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<tr>
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<td></td>
<td>This decline in visual motor integration at year 1 and year 2 was predicted by the baseline performance on the Purdue Pegboard test. This suggests that that early reductions in fine motor speed, possibly due to vincristine and/or acute methotrexate toxicity, lead to reduced visual motor integration.</td>
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<td>The Mathematics Intervention improved mathematics abilities and visual working memory compared to standard care.</td>
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<td></td>
<td>Future studies are needed to translate the Mathematics Intervention into a “virtual” delivery method more readily available to parents and children.</td>
</tr>
</tbody>
</table>
Appendix B

Lexile-to-Grade Correspondence Chart

<table>
<thead>
<tr>
<th>Grade</th>
<th>Text Demand Study 2009 25th percentile to 75th percentile (IQR)</th>
<th>2012 CCSS Text Measures*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>230L to 420L</td>
<td>190L to 530L</td>
</tr>
<tr>
<td>2</td>
<td>450L to 570L</td>
<td>420L to 650L</td>
</tr>
<tr>
<td>3</td>
<td>600L to 730L</td>
<td>520L to 820L</td>
</tr>
<tr>
<td>4</td>
<td>640L to 780L</td>
<td>740L to 940L</td>
</tr>
<tr>
<td>5</td>
<td>730L to 850L</td>
<td>830L to 1010L</td>
</tr>
<tr>
<td>6</td>
<td>860L to 920L</td>
<td>925L to 1070L</td>
</tr>
<tr>
<td>7</td>
<td>880L to 960L</td>
<td>970L to 1120L</td>
</tr>
<tr>
<td>8</td>
<td>900L to 1010L</td>
<td>1010L to 1185L</td>
</tr>
<tr>
<td>9</td>
<td>960L to 1110L</td>
<td>1050L to 1260L</td>
</tr>
<tr>
<td>10</td>
<td>920L to 1120L</td>
<td>1080L to 1335L</td>
</tr>
<tr>
<td>11 and 12</td>
<td>1070L to 1220L</td>
<td>1185L to 1385L</td>
</tr>
</tbody>
</table>
Appendix C

Figure 1: Best Practice Educational Pamphlet

Resources
Leukemia and Lymphoma Society. (2013). Learning and Living with Cancer.

What is ALL?
Acute Lymphoblastic Leukemia (ALL) is a cancer that affects the blood and bone marrow, and is the most common childhood cancer.

How is ALL Treated?
Chemotherapy is the most common treatment method.

Radiation may be used in addition to chemotherapy.

Treatments are becoming extremely successful, with survival rates of 90% for children under 15 years of age. Unfortunately, treatment side effects increase with the increase of survival rates.

Promoting Cognitive Performance in Children Undergoing ALL Treatment

Information and resources for parents
Early and Late Effects of Treatment

**Early effects** are the side effects that occur during treatment, such as hair loss, nausea/vomiting, and fatigue.

**Late Effects** are the effects of cancer that occur after treatment ends.

These late effects can greatly impact your child’s learning and transition back to school, as well as their overall quality of life. Some are noticeable right away, while others can take years to develop.

**Cognitive late effects** (those involving thinking, learning, and memory) are increasingly common:

- Organizational problems (ex: misplaced assignments)
- Difficulty with reading and comprehension
- Slower processing speed (may work slower than peers)
- Decreased visual memory (ex: reading music)
- Difficulty grasping math concepts or remembering math facts

**Other late effects can be physical:** Seizures, hearing or eyesight problems, need for a wheelchair or prosthesis (artificial arm or leg), and neuropathy (numbness, tingling, weakness, and/or pain usually in hands or feet).

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**Is Your Child at an Increased Risk for Experiencing Cognitive Late Effects?**

Not every childhood cancer survivor experiences cognitive late effects, but factors that increase this risk include:

- Young age at time of diagnosis
- Female gender
- Radiation to the whole body or head
- Treatment that involves the central nervous system (brain and spinal cord)
- Certain cancer types, including ALL

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"I need help knowing what to expect after treatment and how to help my child with school."

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**Evaluating Your Child for Late Effects**

Any child who is at risk for developing late effects or who is having difficulty in school should be evaluated by a pediatric psychologist or neuropsychologist. Ask your child’s doctor for a referral.

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**Improvement and Prevention of Cognitive Problems in Children Undergoing ALL Treatment**

Many interventions have proven to be successful in preventing and improving cancer treatment-related cognitive deficits:

- Math interventions improve targeted math skills and visual working memory
- Computerized cognitive training programs improve working memory and attention, and decrease the prevalence of learning problems

**Be an advocate for your child.**

Speak to your child’s social worker and medical team to find out what programs are available in your area.