The Dissertation Committee for Michael Isaac Garcia Certifies that this is the approved version of the following dissertation:

Emotional and Behavioral Late Effects in Pediatric Oncology Survivors

Committee:

Kevin Stark, Co-supervisor

Rachel Robillard, Co-supervisor

Deborah Tharinger

Walt Mercer

Gary Borich

Emotional and Behavioral Late Effects in Pediatric Oncology Survivors

by

Michael Isaac Garcia, B.S., M.A., M.A.

Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

December 2010

Dedication

This dissertation is dedicated to my family and friends who have supported me in life through their actions and countless words of encouragement. Thank you to my parents, Gustavo and Carmel Garcia, and to my sister and brother-in-law, Lauro and Delilah Luera for your love, patience, and support. And to my nephew Lou who is still too young to understand what this is all about, remember that *all* is possible.

Acknowledgements

I would like to express my sincere gratitude to everyone I have encountered in my undergraduate and graduate career. Thank you to Dr. Peg Semrud-Clikeman for opening my eyes to the wonderful field of neuropsychology and to Dr. Rachel Robillard for taking me under her wing over the past few years and opening doors to many invaluable opportunities and experiences. She provided me with unwavering patience, support, and guidance in my growth for which I will be forever grateful. I also appreciate and thank my committee members for your support throughout this project. Thank you to the staff at 'Specially for Children, the LIVESTRONG Survivorship Center, and my fellow colleagues, Daniel Garrison and Amanda Winter, for their invaluable assistance in completing this study.

Emotional and Behavioral Late Effects in Pediatric Oncology Survivors

Michael Isaac Garcia, Ph.D.

The University of Texas at Austin, 2010

Supervisors: Kevin Stark and Rachel Robillard

The most common form of childhood cancer is Acute Lymphoblastic Leukemia (ALL). Patients treated for ALL may experience short- and long-term physiological and cognitive effects due to treatment. However, delayed emotional and behavioral effects in pediatric survivors, as well as risk-factors that may make them more susceptible to developing problems with psychological and behavioral functioning are less understood. Studies investigating pediatric survivors have demonstrated that negative emotional and behavioral late effects can and do occur (Hobbie et al., 2000; Buizer et al. 2006; Novakovic et al., 1996; Mulhern, Wasserman, Friedman, & Fairclough, 1989), and it has been purported that survivors experience higher rates of depression, anxiety and low self-esteem (Koocher, O'Malley, Gogan, & Foster, 1980; Kazak, 1994). Anxiety in particular, has been identified as one of the longest lasting psychological sequelae of cancer (Kazak, 1994). Still, the data on long-term psychological sequelae is mixed, with some studies suggesting healthy, long-term, psychological adjustment (Brown et al., 1992; Fritz, Williams & Amylon, 1988; Greenberg, Kazak, & Meadows, 1989).

This pilot study attempted to investigate emotional and behavioral late effects of cancer as reported by survivors and their caregivers on the Behavior Assessment System for Children, Second Edition (BASC-2). This study also investigated potential risk factors that made it more likely to develop emotional and behavioral late-effects. This study hypothesized that females, those undergoing high intensity chemotherapy, and those starting chemotherapy at an earlier age, would report significantly more internalizing and externalizing problems. Analysis revealed significant differences in reporting of anxiety, depression, attention and hyperactivity symptoms combined based on the age when treatment started. No other significant findings were uncovered; however, in an effort to provide directions for future research, patterns in the data were examined by comparing overall means on BASC-2 subscales. For example, females reported more hyperactive symptoms than males. In general, individuals who started treatment at younger ages reported more difficulty with emotional and behavioral functioning. Additionally, males and females adaptive behavior fell within normal limits. Overall, no BASC-2 mean scores were in the at-risk or clinically significant range of impairment suggesting adequate emotional, behavioral and adaptive functioning overall.

Table of Contents

List of Tables

Chapter I: Introduction

Cancer is the leading cause of death in children under the age of 15. Each year, approximately 12,500 children and adolescents (or 1-2 children per 10,000) will develop some form of malignant cancer (National Childhood Cancer Foundation, 2008 [NCFF]; Daly, Krawl & Brown, 2008). In the 1960's malignant cancers in children were almost always fatal; however, advances in medicine and technology, as well as research in the area of pediatric oncology have resulted in significantly increased rates of survivorship in pediatric cancer patients.

In the 1970's, treatment protocols of central nervous system (CNS) prophylaxis (i.e. the induction of chemotherapy and radiation into the spinal cord) led to an increase in the 5-year survival rate of children with cancer (Waber & Mullenix, 2000). Today, between 80-85% of children diagnosed and treated with cancer exceed the 5-year expected survival rate (Waber & Mullenix, 2000; Daly et al., 2008; Mulhern & Butler, 2005).

The most common form of childhood cancer is Acute Lymphoblastic Leukemia (ALL) which affects approximately 1-3.4 children per 10,000 (Waber & Mullenix, 2000; Ries, Miller & Hankey, 1994). Extant literature varies on the peak age of childhood cancer diagnoses; however, most researchers agree that peak diagnosis typically occurs between the ages of 3 to 5, at a time the child is undergoing significant developmental change (Waber & Mullenix, 2000; Daly et al., 2008).

Presently, children with ALL can expect to be treated with one, or a combination, of the following: systemic chemotherapy (i.e. chemotherapy introduced orally, injected into veins and/or muscle(s) and CNS chemotherapy; in more extreme, high-risk cases where leukemia cells have spread throughout organs or into the brain and spinal cord,

radiation therapy and/or or bone-marrow transplantation may be performed (Daly, et al., 2008).

Although, the increased chance of survival is promising, it poses additional dilemmas, as there are side effects involved when children diagnosed with cancer are often subject to much higher doses of chemotherapy and/or radiation and longer treatment protocols than were common ten years ago (Noll et al., 1999). Furthermore, many current treatment protocols act on the CNS; and consequently, children undergoing these highly toxic treatments (e.g. chemotherapy, radiation) may be more susceptible to developing long-term deficits that have come to be known as *neurocognitive late effects* (primarily typified by problems with attention, learning and memory; Mulhern & Palmer, 2003; Daly et al., 2008; Daly & Brown, 2007). For example, some literature suggests that neurocognitive deficits can result from white matter damage to the brain due to the toxicity of treatment(s), leading to deficits in attention, memory, visuospatial skills, executive function, and emotional status (e.g. changes in personality, apathy, increased levels of anxiety and depression, etc.) (Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000). Chemotherapy and/or radiation introduced into the CNS (in order to destroy cancer cells that may or may not reside in the brain and spinal cord) can also produce neurotoxicity that may result in decline of intellectual functioning and problems with academic achievement (Daly, Kral & Brown, 2008; Daly & Brown, 2007). Despite extensive research in neuropsychological, neurocognitive and cognitive late effects, few investigators have addressed potential psychological and behavioral *late effects* in pediatric cancer survivors (i.e. delayed effects of diagnosis and treatment that manifest months to years after treatment has terminated).

Today, pediatric cancer patients can expect to undergo potent and exhaustive treatment protocols in order to better ensure survival. The question thus becomes, at

what cost are we willing to submit children to highly toxic treatment protocols? Although many have focused on trying to understand neurocognitive late effects, there is an alarming absence of knowledge regarding the effects that can negatively affect the quality of life for survivors – particularly in the areas of emotional and behavioral functioning.

Most studies that have typically investigated these constructs tend to focus on children currently undergoing treatment. A difficulty with this approach is that treatment, along with the traumatic experience of being diagnosed with cancer, can cause numerous transient physical and emotional symptoms of their own, such as motor difficulties, cognitive deficits, increased anxiety, depressive thoughts, irritability, problems with concentration, attention, etc. Additionally, not all effects of treatment, or the experience of having cancer, manifest during or immediately after treatment has terminated; for example, subclinical effects such as cardiac damage due to chemotherapy and infertility can occur years after treatment has been terminated (Schwartz, 1999). Despite this limitation, these studies remain helpful in identifying potential risk factors that may make the possibility of developing late effects more likely in the future.

Although the literature in this area remains scarce, Liang, et al. (2006) have produced one that specifically addressed emotional and behavioral effects in children with cancer. Liang and colleagues compared emotional and behavioral outcomes between Taiwanese children with cancer (who were presently attending school) and healthy controls, (matched by grade and socioeconomic status). Using the Child Behavior Checklist (CBCL; Achenbach, 1983) the investigators found that children with cancer had statistically significant higher scores than controls in the following scales: *withdrawal, depression, hyperactivity/impulsivity, rule-breaking and aggressive behaviors, somatic complaints and thought problems* (Liang et al., 2006).

Studies that have investigated general outcomes for pediatric *survivors*, have similarly demonstrated negative emotional and behavioral late effects of cancer occurring after treatment has terminated and remission established (Hobbie et al. 2000, Buizer et al. 2006, Novakovic et al. 1996; Mulhern, Wasserman, Friedman, & Fairclough, 1989). Some have concluded that survivors have higher rates of depression, anxiety and low self-esteem (Koocher, O'Malley, Gogan, & Foster, 1980; Kazak, 1994). Anxiety in particular, has been identified as one of the longest lasting psychological sequelae of cancer (Kazak, 1994). One particular investigation concluded that 20.5% of young adult survivors in their study met criteria for PTSD.

Still, the data on psychological sequelae is mixed, with some suggesting healthy long-term psychological adjustment (Brown et al., 1992; Fritz, Williams & Amylon, 1988; Greenberg, Kazak, & Meadows, 1989). For example, some studies have purported that survivors generally experience healthy psychosocial adjustment, with some concluding that survivors experience a more positive life outlook, higher motivation to interact with peers, investment in interpersonal relationships, less conduct problems and less substance abuse (Novakovic, et al. 1996, Verrill et al. 2000). Other investigations involving pediatric oncology patients currently in treatment have suggested that children undergoing treatment for cancer are more sociable, less aggressive and generally experience greater social acceptance by peers. (Noll, et al., 1999).

Although it is argued by some that pediatric oncology survivors have healthy psychosocial adjustment, others have argued that survivors employ avoidant behaviors (characteristic of Posttraumatic Stress Disorder [PTSD]), and circumvent situations or environments that may remind them of their cancer experience. This, in turn, is thought to help reduce any threats to self-concept and self-esteem (Bauld, Anderson & Arnold,

1998), making it appear that child survivors have achieved adequate psychosocial adjustment.

Investigations into the *potential* (long-term) behavioral effects of cancer on pediatric patients have also been mixed. For example, Noll, et al. (1999), concluded that peers and teachers rated children with cancer attending public schools as less aggressive and enjoying healthy interpersonal relationships with classmates when compared to normative peers. Unfortunately, as with many other studies, this investigation focused on effects close to the time of treatment, and did not focus on long-term behavioral adjustment.

Another deficit related to behavioral functioning that has been identified numerous times in pediatric cancer *survivors* is a tendency to exhibit attentional difficulties. Some suggest that attentional difficulties are a direct result of white matter damage caused by high-intensity chemotherapy that targets the brain and spinal cord (Buizer, de Sonneville, PhD, van den Heuvel – Eibrink, & Veerman, 2005). White matter damage, for example, is though to lead to deficits in executive function. Because executive function is important for purposeful, goal-directed activity, damage to this area is purported to result in behavioral problems due to a decrease in inhibitory control and personality changes (e.g. increased irritability, aggression, apathy, etc.; Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000). In addition, others suggest that attentional difficulties can drive many observed behavioral problems in the classroom, as well as, lead to academic difficulties (Buizer, et al., 2005).

A small sample of the existing literature has additionally focused on identifying risk factors that make it more likely for a child or adolescent to develop potential problems with emotional states and behavioral adjustment post-treatment. However, the task has proved difficult because many studies use participants with different forms, and

in varying stages of cancer, as well as different types and intensities of treatment modality. The intensity of the prescribed treatment is one of the most acknowledged risk factors in survivorship. For example, the literature has purported that radiation treatment can lead to long-term neurocognitive deficits. Recently, however, high-intensity chemotherapy has also been linked with an increase in neurocognitive deficits due to inadvertent damage of white matter (Buizer, et al., 2005).

Although less clear, gender has also been implicated as a risk factor, with females experiencing a higher rate of overall intellectual cognitive decline than males; although males have been shown to have more significant attentional deficits (Von der Weid, Mosimann, Hirt, et al., 2003). Other researchers have suggested that the age at which diagnosis is made, and treatment initiated, is important in determining emotional and behavioral outcomes. (Although, research regarding the associations between the development of the child and subsequent effects of cancer is clearly mixed). For example, one study concluded that older children and adolescents experience more psychological (i.e. anxiety, depression, poor self-esteem) and psychosocial problems than younger children. Investigators reason that children diagnosed with cancer early in life retain less vivid memories of their experience with cancer, leading to less psychosocial problems and better psychological adjustment long-term (Koocher, O'Malley, Gogan & Foster 1980). Other investigations have demonstrated that adolescents experience better long-term emotional and behavioral outcomes because of their more mature development and higher degree of available coping strategies. Specifically, some believe that younger children use less developmentally mature strategies to cope with high levels of stress. Adolescents, on the other hand, are believed to handle stressors, like cancer, more effectively and efficiently by employing a conglomerate of coping strategies involving both abstract and pragmatic methods; thus it is believed by some that younger children

will ultimately have a more difficult time regulating their emotions and behavior (Band & Weisz, 1988; Worchel, Copeland & Barker, 1987).

It has been stated previously that one of the most significant limitations of published investigations researching the emotional and behavioral late effects of children with cancer is that few have looked at the long-term outcomes for pediatric survivors that may manifest a year or more after treatment has been terminated. In addition, a large portion of the extant literature has focused only on neuropsychological outcomes (Armstrong & Reaman, 2005). Although investigations into neuropsychological and/or neurocognitive deficits is important, it is also beneficial to investigate effects (e.g. emotional and behavioral late effects) that may result from physiological changes in the brain (due to toxic treatment protocols) and/or trauma from the experience of battling/surviving cancer. Additionally, existing research has often focused on investigating late effects using participants with varying forms of cancer and at different stages in the progression of disease and treatment; this makes it difficult to accurately identify emotional and behavioral outcomes specific to the diagnosis and/or treatment. In addition, the ability to focus on specific populations, instead of using a conglomerate of participants, makes it more feasible to identify specific risk factors that may increase the probability of developing emotional and behavioral late effects.

This pilot study will investigate the emotional and behavioral late effects in pediatric survivors of ALL, as well as attempt to identify potential risk factors that may make it more likely to develop these problems. Through the identification of potential late effects and risk-factors, it is possible that the results may provide information useful in developing differentiated psychosocial care protocols that include parents, teachers and the survivors' communities, as well as to improve long-term emotional and behavioral outcomes for pediatric survivors of ALL.

Chapter II: Literature Review

CHILDHOOD CANCERS OVERVIEW

Cancer is the second leading cause of death in the United States, and the first leading cause of death for children under the age of 15 (National Cancer Institute, 2008 [NCI]). Thirty years ago, approximately 30% of children diagnosed with cancer survived into adulthood; thanks to medical and technological advances, that number has increased to approximately 80-85% (National Institute of Health, 2008 [NIH]; Barnes & Harvey, 2006; Waber & Mullenix, 2000; Daly et al., 2008; Mulhern & Butler, 2005).

Cancer (medically known as a *malignant neoplasm*) is a general term for a class of diseases that are characterized by uncontrollable cell growth and replication. Cancerous cells can divide and multiply uncontrollably; they can invade and destroy adjacent tissues (*intrusion*), or can *metastasize* and spread throughout the body via the bloodstream or lymphatic system. The resulting mass of extra cells can sometimes produce tumors. Not all cancers produce tumors, however, as is the case with Leukemia. In addition, not all tumors are cancerous. A *benign* tumor, for example, is not considered a cancer because it does not aggressively and uncontrollably grow, does not intrude on surrounding tissue and does not metastasize (NCI, 2008b).

Leukemia

Leukemia is the most common form of childhood cancer (NCId; NCFF; Barnes & Harvey, 2006). Leukemia is a cancer affecting the blood cells in bone marrow that are responsible for fighting infection. In healthy individuals, bone marrow produces stem cells, or immature cells, which in turn become lymphoid or myeloid cells. Lymphoid cells develop into three different types of white blood cells (called lymphocytes): B lymphocytes that produce antibodies to fight off infection, T lymphocytes which aid B lymphocytes produce antibodies, and "natural killer cells" that target viruses and

cancerous cells (NCI, 2008e). Myeloid cells can mature into three possible blood cell types: red blood cells that deliver oxygen and remove waste from tissues throughout the body, white blood cells responsible for fighting off infection and diseases, or platelets which help promote clotting of blood (NCI, 2008d).

Abnormalities in the way these cells develop can lead to two major types of Leukemia: lymphoblastic leukemia or myelogenous leukemia. In lymphoblastic leukemia, there is an overproduction of lymphocytes (also known as leukemic cells) that do not fight off infection well and prevent the growth of healthy white blood cells, red blood cells, and platelets; all of which are necessary to fight off infection, prevent anemia, and control bleeding (NCI, 2008e). In myeloid leukemia, overproductions of myeloblasts (or immature white blood cells) proliferate and prevent the normal production of healthy white and red blood cells, and platelets (NCI, 2008d).

Lymphoblastic and myelogenous leukemia can be either acute (i.e. rapidly developing) or chronic (i.e. slowly developing), leading to four possible subtypes: Acute Lymphoblastic Leukemia (ALL), Chronic Lymphoblastic Leukemia (CLL), Acute Myelogenous Leukemia (AML) and Chronic Myelogenous Leukemia (CML). Ries, et al. (1999) estimates that of the approximately 3,250 children who are diagnosed with leukemia in the United States each year, approximately 2,400 are diagnosed with ALL (Ries et al., 1999). Between 1990 and 1995, leukemias represented 31% of all cancers diagnosed in children under 15 and 25% of all cancers diagnosed in young adults younger than 20 years of age (Ries et al., 1999). ALL is the most common form of Leukemia in children, accounting for up to as high as 75% of all childhood leukemias (NCCF, 2008). The major types of childhood cancers include leukemia, sarcoma, cancers of the central nervous system, lymphoma, liver cancer, and cancer of the kidneys (National Childhood Cancer Foundation [NCCF], 2008). According to the NCI (2008b), cancer is caused by

abnormalities in genes that are responsible for controlling and regulating cell growth and death. The process of cell death is referred to as *apoptosis* or programmed cell death. Abnormal genes that disrupt the process of normal cell growth and apoptosis can either be inherited or altered by environmental factors. For example, diet and exposure to certain carcinogens (e.g. cancer-causing agents such as tobacco and ultraviolet (UV) radiation from the sun), viruses (e.g. human papillomavirus [HPV], hepatitis B and C [HepB and HepC], and human immunodeficiency virus [HIV]) can each alter genetic material, thereby increasing an individual's risk of developing a malignant neoplasm. An individual can also inherit cancer-promoting gene alterations from their parents (although the predisposition does not assure future cancer development). There is an increasing body of research that indicates the heritability of cancer may be mitigated by complex interactions between the individual's genetic makeup and exposure to cancer-promoting agents in the environment (NCI, 2008c; Pui, 2000).

Treatment

Treatment for leukemia is complex and depends on a variety of factors such as type of leukemia, age at diagnosis, initial white blood count, whether the leukemia is acute or chronic, and whether the leukemia has crossed over into the blood stream and into the CNS (i.e. brain and spinal cord). Generally, however, children with ALL and AML are treated with chemotherapy; some who have more aggressive cancers will also be treated with either whole-body or cranial radiation (Miller, 2007). Although there are clinical trials for new treatments underway, there are 3, generally recognized and utilized, treatment phases for children with leukemia. The first phase is called *induction therapy* and lasts approximately 28 days (Armstrong & Mulhern, 1999). This first stage is also called the remission induction phase because the goal at this stage is to kill 99.9% of cancerous leukemic cells and leave the cancer within the blood and bone marrow into

remission (NCI, 2008e). The second phase is *consolidation therapy*. During this phase, the child receives higher, more intense doses of chemotherapy/radiation requiring hospitalization for "3-4 days every 3 weeks for approximately 6 months." (Armstrong & Mulhern, 1999). The purpose of this stage is to kill any remaining, yet inactive, leukemia cells in order to reduce the chance of relapse (or a reoccurrence of the disease). For children, this phase can last anywhere from 4 to 8 months. The third and final phase is called *maintenance therapy*. During this phase drugs are usually given at lower doses than those given in the first two phases, and usually do not require hospitalization for administration purposes. The third and final phase can continue for up to 2 years, with the primary goal being to prevent the disease from recurring. Throughout treatment, bone marrow aspiration (i.e. biopsies) is performed to definitively follow the progress of treatment. Treatment can be given orally or directly into veins; however at times, patients will receive CNS prophylaxis or intrathecal chemo-and/or radiation therapy (i.e. administration directly into the spinal fluid) in order to kill all leukemia cells which may have reached the brain and spinal cord (NCI, 2000e).

Sometimes, leukemia does not respond to chemotherapy and/or radiation. In such cases, physicians may suggest increasing the intensity of treatment. While more intense and aggressive approaches aim to destroy all abnormal stem and blood cells found within bone marrow, they can also destroy healthy, normal cells. When this happens, the patient may require transplantation of new bone marrow to replace diseased or damaged cells. Additionally, bone marrow transplantations are also considered as primary treatment modalities in cases where the patient requires more aggressive treatment (Herbert Irving Comprehensive Cancer Center, n.d.). Today, the survival rate for children diagnosed with Leukemia has surpassed 80% due to more refined methods of identification and treatment. These include more accurate neuroimaging and mapping of tumors (which has

allowed for more refined surgical removal of tumors), and advanced radiation and chemotherapy treatment protocol development (Armstrong & Reaman, 2005).

Causes of Leukemia

According to the National Cancer Institute, little is known about the cause of leukemia in children; however, there appear to be certain risk factors which may increase the chances of developing this disease. For example, Down Syndrome and exposure to X-rays can increase the chance of being diagnosed with leukemia. Additionally, previous exposure to radiation and chemotherapy, being Caucasian or Hispanic, being male, and having a brother/sister with Leukemia can also increase these chances (NCI, 2008e).

Effects of Acute Lymphoblastic Leukemia

It is well documented that chemotherapy and radiation for leukemia (and numerous other forms of cancer) can cause detrimental side effects. Some of these side effects occur in the presence of ongoing treatment and have been labeled *short-term effects*. Short-term physical effects can include nausea, dizziness, diarrhea, loss of appetite, hair loss, weight gain/loss, fatigue, etc (Novakovik, et al., 1996). Psychological short-term effects such as increased irritability (particularly in children), anxiety, increased depressive symptomatology and overall emotional distress can also occur. Side effects that do not resolve after treatment protocols are completed have been labeled *long-term effects* of cancer. Unfortunately, not all effects of cancer occur during, or immediately after, treatment has been completed; some subclinical effects can manifest years later and are known as *late effects* (Schwartz, 1999).

Differentiating Effects

One of the difficulties inherent in investigating potential late effects of cancer is differentiating between late effects caused by the treatment itself, and late effects due to

the experience of being diagnosed and treated for a potentially life-threatening disease. For example, the lives of children and adolescents diagnosed with cancer can abruptly change; any disruption in their normal routines can cause significant distress, and especially when the stressor is a life-threatening disease. The fear of death and the unknown, frequent hospitalizations, separation from family and friends, and the fear of reoccurrence of their cancer later in life can prove to be an emotionally traumatic experience. The nature of the treatment(s)/procedures that children and adolescents must undergo can prove to be traumatic as well. For example, frequent lumbar punctures (spinal taps), venipunctures, broviac insertions, blood and bone marrow transfusions/transplants are common, and generally unpleasant, procedures that cancer patients must endure.

The cumulative effect of adding these to the already emotionally and physically draining side effects of radiation and chemotherapy (such as nausea, weight gain/loss, fatigue, hair loss and acne) can contribute to overall psychological distress (Pelcovitz, et al., 1998). Kazak (1994) indicates that anxiety relating to memories of cancer diagnosis and treatment experience (e.g. undergoing frequent painful procedures, emotionally and physically draining side-effects of treatment, etc.) remains one of the longest lasting psychological sequelae in pediatric survivors of cancer. Unfortunately, physiological changes due to radiation and/or chemotherapy treatment have been demonstrated to cause changes in personality, apathy, anxiety, and depression (secondary to white matter damage) making the differentiation between cancer diagnosis/experience and treatment difficult to differentiate (Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000).

Effects of Radiation and Chemotherapy on the Central Nervous System

Prior to current advancement in treatment of children with ALL, many were subjected to "whole-brain and spinal *radiation* therapy" (Armstrong & Mulhern, 1999).

Although these procedures were often effective, the use of radiation on young children caused considerable concern about the potentially detrimental short- and long-term side effects of such intense treatment for children. Some investigators questioned the protocol and determined that this method caused significant growth delays and cognitive impairment (Kun, 1997; Waber & Tarbell, 1997). Presently, decline in intellectual ability, secondary to cranial radiation in pediatric cancer patients, is well established in the literature when radiation doses of 18 Gy (Gy=gray, or a unit of absorbed radiation dose) or greater are administered; many of these individuals also experience cognitive and academic difficulties over time, requiring many of them to need special education services and/or additional assistance in postsecondary education and training programs; however, the exact cause of intellectual decline is not clearly understood (Kazak, 1994).

In the late 80's and early 90's, researchers began to focus more heavily on investigating the effects of radiation on the pediatric patient. Studies began to realize that that the developmental stage of the child (specifically the stage of development at which they received treatment), along with the level of radiation, could play a significant play a role in the resulting severity of neurotoxic effects of treatment. For example, some studies found that infants and very young children with brain tumors had significantly lower survival rates than older children (Duffner et al., 1993; Duffner, Cohen, Myers & Heise, 1986; Evans, Jenkins & Sposto, 1990) and were at higher risk for treatment-related neurotoxicity, such as mental retardation and leukoencephalopathy (i.e. destruction of the myelin sheaths that cover nerve fibers/neurons; Davis, Hoffman, Pearl & Braun, 1986).

One particular study found significant stunted development of the spine when children with brain tumors underwent craniospinal radiation; they discovered that there might be a loss in height as high as 9cm when cranial radiation was administered to children less than 1 year of age, and a loss of 5.5cm when administered at 10 years

(Shalet, Gibson, Swindell & Pearson, 1987). Researchers suspect that cognitive late effects are, in part, affected by treatments which negatively impact the development of the central nervous system (CNS; Armstrong & Mulhern, 1999). Additional studies have also documented physical and neurocognitive late effects related to treatment with radiation and/or chemotherapy such as stunted growth, problems with pubertal development, difficulties with cardiac and pulmonary functioning, secondary cancers and deficits in intellectual abilities (Kazak et al., 1997; Meister & Meadows, 1993).

Effects of Alternative Treatment Protocols

In the 1980's, the Pediatric Oncology Group (a now defunct, U.S. and Canadian clinical trial cooperative group) studied the effects of postponing cranial radiation for young children (between the ages of 22 and 36 months at diagnosis) with malignant brain tumors. The investigators found that children whose postoperative chemotherapy treatments were extended, "in order to permit a delay in the delivery of radiation to the developing brain" had significantly less treatment-related neurotoxic effects (Duffner, et al., 1993). The Pediatric Oncology Group further investigated the treatment protocol involving the exposure of the entire CNS to radiation, and subsequently suggested an alternative protocol that consisted of a 3-drug (chemical) "cocktail" of varying chemotherapy agents injected directly into the spinal cord. Although this method still left the CNS vulnerable to insult, it proved to be just as effective for treating the cancer as whole-brain and spinal radiation therapy with less, although still present, neurotoxic effects.

Combination therapies with lower doses of cranial radiation and typical intrathecal and intravenous chemotherapy doses have also been identified in longitudinal studies as causing decline in intellectual and cognitive abilities (Kazak, 1994; Mulhern & Palmer, 2003). A longitudinal study with internal control and comparison groups reported

significant intellectual decline in 24 patients who were assessed with IQ testing pre-treatment and at 1- and 4-years post-treatment. Decline in intellectual functioning was not observed at 1-year post treatment; however significant decline (with a mean loss of 6 to 7 IQ points) were observed at 4-years post-treatment in Full-Scale, Verbal and Performance IQ scores. Twelve of the 24 children had also needed special educational services by the time of their 4-year evaluation; 3 of 12 had repeated a grade. This research suggests that even limited dosages of radiation appear to cause neurocognitive toxicity (Mulhern & Palmer, 2003).

Consequently, many practitioners have begun to move away from the use of radiation to treat ALL in children and have moved to relatively less toxic forms of treatment such as chemotherapy. Presently, chemotherapy treatment restricted to systemic chemotherapy (i.e. injected into a vein and/or administered orally) is the method of choice for treating ALL in children; however, CNS preventative therapy (or chemotherapy that exposes the CNS to radiation and/or chemotherapy agents) is sometimes utilized if the cancer is more aggressive than normal. Because more aggressive cancers can cause leukemic cells to migrate to organ systems, as well as to the brain and spinal cord, more intensified treatment is required to ensure that all cancerous cells are destroyed (Mulhern & Palmer, 2003).

NEUROTOXICITY OF TREATMENT

Although little is known about chemotherapy's short- and long-term effects, it has been shown to cause acute, subacute, and delayed neurotoxic effects. For example, acute (but reversible) neurotoxicity occurs in approximately 5.8-18.4% of children undergoing chemotherapy treatment for ALL during the consolidation (or intensification) stage of treatment (Mahoney, Shuster, Nitschke, et al., 1998; Lo Nigro, Di Cataldo, & Schiliro 2000) resulting from intrathecal methotrexate (a common chemotherapy agent). Acute

neurological symptoms may manifest as short-term left-arm weakness and aphasias (such as writing difficulty and inability to speak). However, most will experience seizures as a result of acute neurotoxicity (Mahoney, Shuster, Nitschke, et al., 1998). These manifestations are thought to be symptoms of cytotoxic edema (i.e. excess fluid in cells throughout the brain), secondary to intrathecal methotrexate, that cause excess fluid in cells throughout the brain. Neurotoxic effects are reported to worsen significantly when accompanied by cranial radiation (Mahoney, Shuster, Nitschke, et al., 1998; Armstrong & Mulhern, 1999).

A similar study investigated 30 ALL survivors who had undergone CNS treatment with chemotherapy only. The children were administered neuropsychological evaluations at various intervals, up to 4-years post-diagnosis. At 4-year post-diagnosis, IQ scores remained stable; however, arithmetic achievement, verbal fluency and visual-motor skills had decreased significantly. This indicated to the investigators that even methotrexate alone was enough to harm the CNS. An additional study investigating the neurocognitive late effects of pediatric ALL survivors treated with chemotherapy only also measured deficits in the areas of Performance IQ, perceptual organization, and freedom from distractibility scores (Mulhern & Palmer, 2003).

Treatment for childhood cancer has progressed significantly throughout the years; however, many of the treatments continue to pose a significant threat to neurocognitive abilities later in life. The severity of neurocognitive late effects experienced by pediatric patients can differ because of the variation in the severity of their cancer, age and developmental level at diagnosis and start of treatment, the type(s) of treatment required (e.g. chemotherapy, radiation, surgical resection of tumors, etc.), and the intensity and length of treatment (Mulhern & Palmer, 2003). Despite the variation in the spectrum of

neurocognitive deficits experienced, the incidence of late effects remains alarmingly high.

NEUROLOGICAL EFFECTS OF TREATMENT

Although each pediatric oncology patient may be affected differently by individual-specific factors, researchers agree and suspect that cognitive late effects are largely affected by treatments that negatively impact the development of the CNS (Armstrong & Mulhern, 1999). Neurotoxic insult to the CNS can increase the chance that pediatric oncology patients will develop both short- and long-term cognitive deficits in memory, learning, thinking and processing speed (Mulhern & Palmer, 2003). Although current research indicates that neurocognitive effects tend to occur in the presence of neurotoxic insult to the CNS, the knowledge about exact causes and mechanisms that lead to such deficits is limited; according to Mulhern and Palmer (2003), neurocognitive late effects will be reduced or eliminated altogether only when we can pinpoint the biological and developmental underpinnings of such effects

Despite the limited knowledge about the exact causes of neurocognitive late effects, research utilizing neuro-imaging has shown that neuropathological changes (i.e. changes in nervous system [brain and spinal cord] brain tissue) due to chemotherapy and radiation treatment can promote the development of neurocognitive, emotional and behavioral late effects later in life (Mulhern & Palmer, 2003).

A study conducted by Kingma, Mooyart, Lamps, Nieuwenhuizen and Wilmink (1993) investigated whether treatments for ALL in children resulted in structural changes to the brain and neuropsychological deficits. The study included 35 children between the ages of 7-8, diagnosed with ALL who had been treated with cranial radiation (i.e. radiation therapy to the head intended to prevent leukemic cells from spreading) and intrathecal (i.e. injection of chemotherapy directly into the spinal fluid) and intravenous

methotrexate (a chemotherapy agent). All participants received magnetic resonance imaging (MRI) and neuropsychological assessments. Results from this study indicated that 51% of participants had "definitely abnormal" MRI's, while 17% had "probably abnormal" MRI's. The investigators also discovered that neuropsychological scores were significantly lower compared to a comparison group in the following four areas: measures of intelligence, verbal auditory memory, visual motor integration and fine motor functioning. Abnormalities seen in MRI's were not related to age at diagnosis; however, lower neuropsychological performance on the above mentioned areas were correlated with higher doses of cranial radiation and younger age at diagnosis. Of particular note was that many of the participants developed *toxic leukoencephalopathy* (i.e. damage to white matter of the brain due to ingested toxins) (Kingma et al., 1993). Others have demonstrated similar results and implicated a link between combination radiation and chemotherapy treatments and leukoencephalopathy (Price, 1983). According to some, symptoms of white matter damage (which can manifest itself as focal seizures, ataxia, fatigue, cognitive decline, slurred speech and memory loss) may not manifest until after the fourth of fifth month of receiving cranial radiation treatment (Stehbens, et al. 1991).

White Matter Damage

White matter makes up half of the cerebrum, or forebrain; relative to the evolution of human beings, the cerebrum is the "newest" part of the brain. White matter is composed of nerve fibers called neurons; the neurons contain axons that are insulated by a fatty protein called myelin; this myelin sheath insulates axons and helps them transmit electrical impulses from axon to axon speedily. The myelination of axons continues through birth and into the third decade of life (Mulhern & Palmer, 2003). Six thin layers of neurons called the cerebral cortex cover the cerebrum's surface. The white matter of

the cerebrum consists of interhemispheric and intrahemispheric tracts that connect cortical and subcortical regions of gray matter to initiate higher cerebral functions (Filley & Leinschmidt-Demasters, 2001). Unlike white matter that is composed of nerve cell axons, gray matter contains nerve cell bodies. Gray matter throughout the brain mediates higher cerebral functions while white matter forms connections between structures that bring about these activities (Schiffer, Rao & Fogel, 2003).

Effects of White Matter Damage

White matter is particularly susceptible to damage from cranial radiation therapy because it can halt the developmental process of the myelination of axons (Mulhern & Palmer, 2003) leading to demyelization (i.e. the loss of myelin). If white matter is damaged, then the neurons and axons are not able to readily and speedily transmit information between brain structures and send electrical impulses throughout the body. Other studies have clearly shown the link between radiation treatment and leukoencephalopathy (Davis, Hoffman, Pearl & Braun, 1986; Kingma et al., 1993). However, white matter damage is not isolated to radiation treatment alone and has also been observed in patients who underwent high-dose chemotherapy treatment (Mulhern & Palmer, 2003).

According to Filley and Leinschmidt-Demasters (2001) white matter is known to play a large role in movement, sensation and vision; however, the literature has also made associations between damage to white matter and problems with cognition and emotions. Research about the effects of toxic leukoencephalopathy have become so well documented that researchers like Filley and Leinschmidt-Demasters (2001) now suggest that the appearance of deficits in mental status is crucial for the appropriate diagnosis of toxic leukoencephalopathy. For example, they state that, “Deficits in attention, memory, visuospatial skills, executive function, and emotional status in the absence of aphasia (a

loss of the ability to produce and/or comprehend language) can suggest the occurrence of white-matter damage" (Filley & Leinschmidt, 2001, pg. 427). They also propose that personality and emotional changes, such as apathy, depression and anxiety, are common symptoms of white matter damage (Filley & Leinschmidt, 2001). Other research investigating resulting deficits from neurological toxicity, (in particular white matter damage), have demonstrated interruptions of higher cerebral functions, such as problems with attention, memory, personality changes, dementia, and in rare cases, coma and death (Hill, Cooper & Perry, 2000).

Additional Neurological Damage Due to Treatment

Additional research indicates that white matter rich in myelin is particularly abundant in the right frontal lobe. Functions associated with the right frontal lobes, such as attention and visuospatial abilities can consequently be affected by damage to this area (Mulhern & Palmer, 2003). Damage to white matter may thus be one possible explanation for the significant deficits in neuropsychological functioning for these individuals.

Researchers have also observed brain tissue abnormalities such as a more diffuse blood-brain barrier, microvascular occlusion, and calcifications in cortical gray matter and the basal ganglia in patients undergoing cerebral radiation (Mulhern & Palmer, 2003). Calcifications in the basal ganglia do not often occur in young, healthy individuals. Typically, calcifications in the basal ganglia develop during the third to fifth decade and manifest as movement/motor, and neurocognitive difficulties such as problems with memory, concentration, personality/behavioral changes, increased fatigue, problems with gait and coordination, and slow or slurred speech (Geschwind, Loginov & Stern, 1999; Manyam, Walters, & Narla, 2001).

EMOTIONAL AND BEHAVIORAL EFFECTS OF TREATMENT

The Children's Oncology Group (COG) was formed in the 1980's to address and promote pediatric cancer awareness and research across multiple disciplines. The COG's goal is to advance not only the survival rate of children with cancer, but to improve long-term quality of life for survivors and their families. In order to accomplish this, the group endorses combining the knowledge gained in controlled clinical trials of treatment protocols with behavioral and psychosocial research so that questions and answers addressed in the future can have widespread clinical relevance.

The COG indicates that in the past 25 years, the primary focus of cancer's late effects in children has been on physiological and neurocognitive outcomes (Armstrong & Reaman, 2005). Similarly, Kazak (1994) indicates that the largest body of research on late effects of cancer in children has focused heavily on neuropsychological late effects resulting from cranial radiation. Despite the limited research on psychological and behavioral late effects in child survivors of pediatric cancer, the COG suggest that psychological outcomes are crucial in order to advance the understanding of "psychological processes in humans related to stress and coping, brain development, contributions of family and health systems to children's development and psychological adaptation to trauma" (Armstrong & Reaman, 2005, pg. 93). Investigating and documenting emotional and behavioral late effects due to cancer treatment as well as the traumatic experience of being diagnosed with cancer, can thus provide knowledge helpful for identifying potential risk factors of negative emotional and behavioral sequelae, leading to improved prevention and intervention techniques and protocols.

Emotional Late Effects

There is a large disconnect in the literature between neuropsychological late effects of cancer treatment in children and long-term psychological sequelae. Despite the

limited knowledge of emotional and behavioral consequences of cancer diagnosis and treatment, a few investigators have aimed to address and contribute to this very important issue. Although it would seem intuitive to believe that being diagnosed and treated for such a life-threatening disease (such as cancer) might result in negative, long-term psychological impact on survivors, this is not always the case. Various researchers for example, have noted that long-term childhood survivors of cancer experience healthy psychosocial adjustment (Brown et al., 1992; Fritz, Williams & Amylon, 1988; Greenberg, Kazak, & Meadows, 1989). Noll (1999) for example, noted that children currently undergoing treatment for ALL were rated by their peers and teachers as being more likeable and sociable; they were also similar to case controls on measures of emotional well-being suggesting considerable psychological hardiness. This study explores the possibility that not all children who experience life-threatening diseases are subject to negative effects of cancer diagnosis and treatment.

Conversely, other studies investigating similar populations (i.e. children currently receiving chemotherapy treatment for various forms of childhood cancers) have suggested increased risks for problems in two particular domains: social adjustment with peers (e.g. sociability, leadership abilities, aggressiveness towards peers) and emotional well-being (e.g. anxiety, aggression, depression, feelings of rejection) (Deasy-Spinetta, 1981; Katz, Rubinstein, Hubert, & Blew 1988; Larcombe et al., 1991; Bennet, 1994; Canning, Hanser, Shade, & Boyce, 1992; Dolgin, Katz, Zeltzer, & Landsverk, 1989; Kashani, & Hakami, 1982).

Unfortunately, one of the more notable limitations of these (and many other) studies is that results are often based on ratings from children currently undergoing treatment for cancer and do not adequately address psychological late effects after treatment has terminated and remission status is established. Despite this limitation,

studies investigating immediate psychological and behavioral effects may help to identify potential risk factors that can increase and intensify the probability of experiencing psychological and behavioral late effects of diagnosis, the overall cancer experience, and treatment.

One of the earliest studies to investigate the late-psychological sequelae of cancer was conducted in 1980 when significant changes in medical technology and the advent of more effective treatment and surgery changed the prognosis of pediatric cancer patients from "inevitable gloom to guarded hope" (Koocher, O'Malley, Gogan, & Foster, 1980). Koocher et al. (1980) investigated global psychosocial adjustment of 115 *former pediatric cancer survivors* who were 18 years or younger at diagnosis, in remission, and off cancer treatment for one year. This sample was also at least 60 months beyond initial diagnosis. The researchers demonstrated that a significant portion of pediatric cancer survivors experienced residual psychological sequelae such as depression, anxiety and low self-esteem. Anxiety in particular has been found to be a long-lasting problem in pediatric cancer survivors.

Kazak (1994) has suggested that the most lasting psychological outcomes related to childhood survivors of cancer is anxiety relating to memories of their experience with cancer and fears over the possible recurrence of disease. Kazak noted that even very young children maintain vivid recollections of their treatment experience, their understanding of which evolves as they mature potentially leading to varied psychological outcomes. The reason for persistent anxiety beyond treatment and remission is not well understood but is evident in other studies as well. Another such investigation (Koocher, 1984) found that even after treatment ended and remission was established, children tended to stress about the potential recurrence of their illness. Childhood cancer survivors often become hypervigilant to lumps or other signs that are

symptomatic of cancer. Furthermore, it has been demonstrated that anniversaries relating to the dates of diagnosis, dates treatment began, etc. are often anxiety-invoking reminders about cancer experiences. Although Kazak (1994) reported that anxiety is the most lasting psychological sequelae of cancer, Peck (1979) suggests that anxiety dissipates over time.

The persistence of anxiety is further exemplified by a study that (Mulhern et al., 1989) found 1/3 of child cancer survivors (participants >15 years-old) were rated by their parents as having frequent somatic complaints that lacked any known medical cause. The investigators hypothesized that somatic complaints were either the result of parents' lack of awareness regarding true, medically relevant symptoms or caused by hypochondrical-tendencies on part of the child cancer survivors due to their experience with a life-threatening illness. Although anxiety was not specifically measured by this particular study, somatic complaints are often defined as secondary symptoms of anxiety (Mulhern et al., 1989).

Anxiety is also inherent in Posttraumatic Stress Disorder (PTSD). PTSD symptoms can manifest in individuals after exposure to traumatic events, with war the most common event referred to when talking about PTSD. However, PTSD is not only limited to experiences concerning war and may also occur in the face of life-threatening disease, among other things. The revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychological Association, 2000) addressed the traumatic experience (for both child and parent) of being diagnosed and undergoing treatment for a potentially fatal disease, such as cancer, and identified the experience as "an event sufficiently traumatic to precipitate PTSD (Hobbie et al., 2000). Hobbie et al. (2000) performed a study investigating posttraumatic symptoms in 78, young adult (18-40 year-old) pediatric cancer survivors. The investigation also aimed to

address any potential associations between posttraumatic stress disorder (PTSD) symptoms and anxiety, psychological distress, perceptions of illness and treatment. Analysis of the data revealed that 20.5% of childhood cancer survivors met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for PTSD. They also exhibited clinically significant levels of intrusive and avoidant symptoms. Participants also reported higher state and trait anxiety, had elevated perceived current life-threat symptoms, more intense treatment histories, and elevated levels of psychological distress, (as compared to those participants who did not have PTSD; Hobbie et al., 2000).

Earlier investigations (Barakat, Kazak, & Meadows, 1997) investigated potential posttraumatic stress in child and adolescent survivors of childhood cancer (8-19) and discovered that 4.5% of them met criteria for PTSD; however, the difference in PTSD symptoms was not significantly different from controls (i.e. children who had never been ill). Despite this finding, further analysis revealed that higher PTSD symptoms were associated with higher trait anxiety. The investigators suggest that perhaps trait anxiety may not be a symptom of PTSD itself, but a characteristic that may indicate a propensity for developing the disorder in the future (Hobbie, 2000).

A limitation of existing studies investigating potential emotional and behavioral late-effects in children is that they do not appear to distinguish between different forms of cancer. Some of the studies cited here, for example (Mulhern et al., 1989; Noll et al., 1999) use populations with a variety of forms of cancer making it difficult for the investigators to conclude that specific types of psychological late-effects are related to certain types of cancers.

Behavioral Late Effects

Excessive behavioral problems have been demonstrated previously in children with ALL; however, these investigations studied children who underwent cranial

radiation (Buizer et al., 2006). Studies investigating behavioral outcomes in children with ALL who were treated with chemotherapy are limited. One such study, however, was conducted on pediatric patients ages 4-18 who had terminated chemotherapy treatment for ALL at least one year prior (Buizer et al., 2006). Using the Child Behavior Check List (CBCL), the investigators discovered that when compared to children with Wilm's tumor (who did not undergo chemotherapy treatment) and sibling controls, the ALL group demonstrated significantly more behavioral and educational problems. Parents reported significantly more behavior problems in the ALL group that were mainly attributed to internalizing and attention deficits. Teachers, on the other hand, reported more externalizing (behavioral) problems in ALL survivors. Despite the lack of agreement between parents and teachers, the authors suggest that attentional difficulties appear to be a source of many observed behavioral problems, as well as academic underperformance. They also observed that poor attention (as measured by neuropsychological tests) was correlated with more teacher-reported behavior problems and lower school performance scores in the classroom setting (Buizer et al., 2006).

Prior to this study (Buizer et al., 2006), limited research had suggested that child survivors of cancer generally do not develop behavioral problems. Noll (1999) investigated the social, emotional and behavioral functioning of children currently undergoing treatment for cancer; he discovered that participants were rated by teachers and peers as less aggressive and were generally more popular in social circles. Noll (1999) purported that children in these undeniably stressful circumstances are often surrounded by family and medical support thereby increasing their social awareness and functioning. This can in turn lead to favorable social interaction with peers. Although children did not report any significant emotional problems with depression, anxiety, loneliness, and self-concept, they did report significantly less satisfaction with their

athletic ability. Although these particular participants were still undergoing treatment at the time they participated in this study, Noll (1999) suggests that their less aggressive behaviors (as rated by peers and teachers) were the result of physical limitations due to the effects of chemotherapy and/or radiation. The explanation for this was that if they are tired and worn out, they are less likely to be engage in verbal or physical aggression. Kazak (1994) notes, however, that although children may have a present understanding of their disease and treatment, young children's understanding of their experience and future life-altering consequence evolves as they mature and can lead to much different outcomes in terms of behavior and overall adjustment years later.

Despite Noll's (1999) findings, they did not address the *long-term* adjustment of these individuals in terms of their behavior. Additionally, it did not adequately address potential difficulties with attention, which Buizer et al. (2006) observed, and which has been shown can be a direct result of white matter damage to the brain; damage that can occur, not only from cranial radiation, but from high-dose chemotherapy agents (Mulhern & Palmer, 2003). Although attention deficits may not initially appear to be as serious behavior problems, as are aggression and other conduct problems, problems with attention can lead to frequent disruptions in the classroom, poorer decision-making abilities, frustration, irritability, low self-esteem and anti-social behavior (Eisen, 2007).

Social and behavioral problems were also identified in a survey of social competence and behavioral outcomes of childhood cancer survivors conducted at St. Jude Children's Research Hospital (Mulhern, et al., 1989). Participants included 183 subjects who were seen at their annual visit to the St. Jude's After Completion Therapy Clinic. To qualify, participants had to be free of their disease, 5 years from the time of their diagnosis, and 2 or more years from the completion of therapy. All participants were children under the age of 15. The participants' parents completed a psychological

inventory called the Child Behavior Checklist (CBCL), a measure of recent (6 months prior) social functioning and behavioral problems for children ages 4 through 16. The CBCL is used to measure social and behavioral problems; it does not, however, identify variability in each measured domain within the range of normal childhood behavior. The findings reported that child survivors of various types of cancer (e.g. ALL [45% of participants], Wilm's Tumor, [12% of participants], retinoblastoma [11% of participants], neuroblastoma, [10% of participants]) had three to four times higher incidences of social and behavioral problems compared to normative findings in the general population. Somatic complaints "of undetermined origin" were the most frequently reported symptoms (Mulhern et al., 1989).

ACADEMIC LATE EFFECTS

Academic problems resulting from cancer diagnosis and treatment are documented; however, unlike neurocognitive and psychological effects that have been directly attributed to diagnosis and treatment, academic problems are often presented as secondary effects of prolonged absence from school and functional disabilities resulting from treatment and diagnosis (Mulhern et al., 1989). Functional disabilities are generally disabilities which: prevent individuals from performing various physical activities, cause significant sensory impairment (e.g. vision/hearing impairments), cause symptoms related to serious mental illness that interfere with daily activities (within the past year), require long-term care and/or assistive devices, and lead to developmental delays (Mulhern et al., 1989; Jans, Stoddard, Kraus, 2004). Other studies have found that up to 30% of childhood cancer survivors had experienced academic problems such as difficulty in school, learning disabilities and grade retention (Mulhern et al., 1989; Lansky et al., 1986).

Sick children often miss school due to acute side effects of treatment such as nausea, fatigue, etc. Increased absences can cause children to fall further behind academically when compared to healthy peers. Mulhern et al. (1989) indicates that children with leukemia will miss up to 42% of the school year, a rate that remains significant up to 3 years post-diagnosis. In addition, the physical and emotional stress that treatment, such as chemotherapy and radiation will often negatively affect peer relationships (Armstrong & Mulhern, 1999). Armstrong & Mulhern (1999) also suggest that sick children are often subject to inappropriate educational planning and instruction, particularly when they are reintegrated back into schools. For example, a child who begins to experience increased fatigue and/or irritability should not be subject to the same demands as other children in the classroom. In this case, homebound instruction may be appropriate. However, a child with cancer undergoing treatment with minimal side effects should be held to the same academic standards in order to ensure appropriate academic progress. These nuances of academic planning are often ignored, or are thought to be unnecessary, as educators typically have very little experience, or knowledge about working with this population.

DEVELOPMENTAL DIFFERENCES IN COPING

As cancer survivors age and enter into adulthood, they may discover physical and/or psychological deficits and intellectual challenges, which may not have been encountered before. For example, neurocognitive deficits may prevent a cancer survivor from completing college or obtaining an occupation that may have once been a possibility before cancer. The stress associated with not being able to fully function in the world as they would have expected could also lead to psychological illness, such as depression and anxiety. In addition, physiological late effects, including cardiac damage due to chemotherapy, recurrence of cancer, or infertility can add to the psychological

distress experienced (Schwartz, 1999). If a child survivor of cancer is in perpetual fear that the disease will return, adjusting to life after cancer may be a very difficult challenge, potentially leading to psychological sequelae like depression. This does not imply, however, that all children and adolescents who are diagnosed with cancer will experience negative emotional and behavioral problems associated with their experience and/or treatment.

Understanding how children and adolescents adjust psychologically and behaviorally to terminal illnesses like cancer requires not only an investigation into the physiological course and effects of treatment, but also requires researchers to study the way afflicted individuals respond to stress and coping related to their illness. To date, many studies have investigated how chronic illness stresses and overloads existing coping strategies. However, aside from investigating specific coping strategies or themes, few studies have developed or investigated theoretical frameworks of stress and coping to help elucidate why some childhood cancer survivors adjust better (emotionally and behaviorally) than others.

Stress and Coping

The term "stress" and its meaning have produced considerable debate over the years, with many in the literature arguing about its basic tenants (Berry, Kim, Minde, Mok, 1987). Although there are numerous definitions and conceptual models on stress (Scott and Howard, 1970), for the purpose of this study, stress is defined as any physiological or psychological response of an organism to stressors in the environment. In order for normal functioning to occur, the stress must be reduced or coping should result in order for the organism to adapt to his or her environment satisfactorily (Berry et al., 1987). According to Decker (2006), coping can be defined as the cognitive and behavioral strategies or responses that a person utilizes in order to manage stressful

external and/or internal stimuli which tax and overload existing resources. Coping is said to be learned, rather than instinctual and is molded and modeled by significant others (Zeitlin, 1985).

Part of understanding stress and coping in child and adolescent survivors of cancer requires researchers to investigate models of stress and coping from a developmental perspective (Decker, 2006). For example, children and adolescents undergoing invasive, painful, exhausting and lengthy treatments do so at a time when significant developmental changes are taking place. These changes, however, vary significantly depending on the age at which diagnosis and treatment begins.

Adolescents are particularly vulnerable to the psychological distress experienced during a chronic stressor such as cancer (Pelcovitz et al., 1998; Burgess, 1985; Kulka et al., 1990; van der Kolk, 1985). It is during this period of development that normal, healthy adolescents begin to form their own identity and start to establish some autonomy from parents; however, adolescents with cancer are instead forced to become more dependent on family and hospital staff. This forced regression to dependency, at a time when adolescents typically begin to assert their independence, can cause considerable distress and resentment. Adolescents with cancer often report that their parents are overly protective; although this is a common reaction from parents with children who are experiencing a life-threatening disease (Pelcovitz et al., 1998). Interacting with similar-aged peers also becomes an important part of life during this stage; adolescents with cancer, however, are often subject to frequent hospitalizations and are consequently separated from peers leading to feelings of isolation (Pelcovitz et al., 1998).

Cancer presents a unique challenge to adolescents because it exercises their ability to cope with a chronically stressful situation that is of a magnitude that many have never experienced. The effectiveness of coping styles determines whether or not

adolescents are able to decrease, and cope with, the impact of their stress. In order to do this, Decker (2006) suggests that adolescents must effectively manage their behavior and emotions by thinking in ways they may not have previously attempted. Effective management of stressors such as serious and chronic illness can subsequently determine short- and long-term "social, cognitive and personality development and adaptation" (Decker, 2006, pg. 124).

A Model of Coping

Decker (2006) attempted a metanalysis of the literature concerning coping in children and adolescents with cancer. Of the 12 studies reviewed, only 3 incorporated theoretical frameworks; of these 3 studies, 2 utilized Lazarus and Folkman's stress coping theoretical framework (described below). Decker's review of the 12 studies demonstrated inconsistencies in the coping strategies that children and adolescents seem to employ. Of the various types of coping described (e.g. thinking positive, engaging in distracting activities, self-talk, crying, laughing, asking questions about procedures, seeking the touch of a parent or nurse, gritting teeth, etc.), the most common strategies used by children and adolescents with cancer seem to be problem- and emotion- focused. However, analysis of the studies resulted in inconsistent findings with some studies indicating more problem-focused coping and others finding the utilization of more emotion-focused coping strategies.

Despite the inconsistency in the results of Decker's (2006) analysis, the identified forerunners in the field of stress and coping are Lazarus and Folkman (1984). The Lazarus and Folkman model (based primarily on cognitive appraisal) delineates between two categories of coping behavior: problem-focused and emotion-focused. Problem-focused coping describes efforts to identify and target the stressor(s) in an attempt to change things in the external environment or one's own behavior. Emotion-focused

coping, on the other hand, involves cognitive restructuring in order to reduce the impact of negative emotional states (Lazarus & Folkman, 1984). Thus, the aim of emotion-focused coping is not to physically change their actual situation (e.g. "I have cancer"), rather it allows individuals to alter the perception of the situation.

Some have argued that Lazarus and Folkman's (1984) model is overly simplistic because coping skills vary from individual to the next; what may work for one person may have no impact on reducing distress for another. Indeed, coping is a complex process that involves the use of strategies to regulate levels of stress and mediate psychological sequelae. An individual's response to stress may depend on their coping resources, which can be psychological (i.e. personal characteristics, attitudes, cognitive/core beliefs) or social (i.e. social network such as friends, family, medical staff, religious affiliation) in nature. Additionally, an individual's coping style and coping efforts (i.e. cognitive or behavioral actions in order to reduce stress) can also determine the level of adjustment that is made in response to stress (Compas, 1987a) Despite the simplicity and limitation of Lazarus and Folkman's (1984) theoretical model of coping, it remains an important framework that can help explain developmental differences in regards to stress and coping of children and adolescents with cancer.

The way a child or adolescent copes with a life-threatening illness may also be greatly influenced by the developmental maturity of the child at the onset of disease. For example, the necessary skills for problem-focused coping are postulated to develop between the ages of 8-11. Children at this age are not as aware or knowledgeable about their internal emotional states. Thus, it seems appropriate to expect that they would utilize more problem-solving oriented approaches to stressful situations. In addition, because problem-solving skills are more overt, thus more observable, young children may much more easily learn these skills by observing older adults. Emotion-focused

coping, however, is thought of as a more developmentally mature strategy for coping because it requires a certain level of internal awareness that begins to develop in older children (>12) and young adolescents. The use of emotion-focused coping in older children may become more pronounced when they discover that emotions can be self-regulated. Unlike young children who learn problem-focused strategies from observing others, emotion-focused coping is less overt and not easily observable or translatable (Compas, Banez, Malcarne & Worsham, 1991; Compas et al., 1988; Compas & Worsham, 1991; Wertleib et al., 1987).

Other studies have also demonstrated that older children and adolescents tend to think more abstractly and utilize more cognitive-based coping strategies (Band & Weisz, 1988; Worchel, Copeland & Barker, 1987). However, in another study, the differences in coping strategies observed between adolescents and young adults were not significant or as pronounced. This suggests that developmental differences in coping appear to level off by late adolescence when developmental differences between adolescents and young adults diminish (Compas & Worsham, 1991; Compas et al., 1991).

Some investigators believe that emotion-focused problem solving is more beneficial in response to stressful situations, in particular with cancer patients, because problem-focused coping cannot change the physical effects of the disease (i.e. nausea, hair loss, fatigue, etc.) (Bull & Drotar, 1991; Folkman, 1984; Wertlieb, Weigel, & Feldstein, 1987). Despite the perceived benefits of cognitively restructuring negative beliefs and attitudes regarding such a physically debilitating illness, not all research has demonstrated that emotion-focused coping correlates well with increased age. Some studies have shown no difference at all (Altshuler & Ruble, 1989; Band, 1990) with others indicating that increased age leads to an increase in problem-focused coping (Compas et al., 1991).

Complexity of Coping

Perhaps the variability in findings is a result of the complexity involved with coping. It is far too simplistic to believe that coping styles used by individuals is an all or nothing proposition. Utilizing one strategy over another (emotion-focused vs. problem-focused) may not be entirely beneficial as it would be to use a conglomerate of strategies. For example, Moos (1976) and Zeitlin (1985) suggest that individuals' coping strategies are much more complex. As individuals age, coping behaviors change, and are altered or discarded in order to meet the demands of the stressor in question. Although problem-focused coping may not directly change the physical effects of cancer, problem solving skills, such as identification of the stressor, identifying different strategies that may help reduce the impact of the stressor, evaluating the effectiveness of those strategies and coming up with alternatives, are necessary for both problem- and emotion-focused coping. In addition, although children begin to think more abstractly in their approach to coping as they age, it is unlikely that the problem solving abilities they develop in childhood would be discarded in adolescence; rather, it would seem more reasonable to believe that adolescents and adults would mesh their coping styles into a conglomerate of strategies involving both pragmatic and abstract ways to cope with significant stressors.

Despite investigations into developmental differences of coping styles in response to life-threatening stressors like cancer, current available research has focused on the way individuals respond to *current* stressors and not how coping styles may influence the development of emotional and/or behavioral at a much later time, especially in children and adolescent survivors of cancer. Using the existing literature, one might argue that adolescents who are diagnosed with cancer at age 16 might have more complex coping styles/strategies at their disposal than a 7-year-old, inherently making coping with a life-threatening disease less stressful and more manageable. Consequently, the experience of

having cancer as a young child (when coping styles are already limited) may be remembered as more traumatic and less manageable, ultimately leading to more problematic emotional and/or behavioral adjustment difficulties down the road.

Using the existing literature, it could be purported that younger pediatric survivors' *locus of control* could be potentially impacted by their inability to sufficiently cope with a stressor like cancer. If this is indeed the case, then younger children may learn to attribute more external events (e.g. luck, God, etc.) to the outcome of their illness. This perceived absence of control, may consequently lead some of these individuals to feel and act helpless when future negative life events arise, even if it was possible to change the outcome of some unpleasant or harmful situation. Seligman (1975) refers to this as learned helplessness and suggests this theory can lead to neurovegetative symptoms of depression and other mental health problems (Seligman & Maier, 1967).

It would be beneficial for investigators to further study whether experiencing, coping and surviving cancer at different developmental stages would result in better long-term psychological and behavioral outcomes later in life. Kazak (1994) states that the longest lasting psychological sequelae for child survivors of cancer are often anxiety and posttraumatic symptoms regarding the cancer experience. Subsequently, if the trauma and stress experienced is diminished through complex coping mechanisms, then perhaps anxiety associated with illness might be less severe and have less impact on psychological and behavioral characteristics for adolescents than for children (who are developmentally limited in these areas).

Although it is plausible that children and adolescents' response to stress can determine later psychological and behavioral sequelae, it is not the only factor involved in determining long-term psychological and behavioral late effects. Specific characteristics that can exacerbate or reduce stress experienced by children with chronic

illness have been identified to include: illness specific characteristics such as severity, course of illness and the degree of handicap that the illness imposes; personal aspects of the child and adolescent such as age of onset of illness, temperament, premorbid intellectual functioning, and premorbid social and emotional adjustment; family resources and dynamics such as openness of communication, cohesion, adaptability to change and problem solving skills; extra-familial support systems such as support from extended family, friends and medical staff (Melamed, Siegel & Johnson, 1988). A web of stressors can thus interact in complex ways to determine the child or adolescent's adaptive coping choices during and after their experience with cancer. The way a person copes may thus depend on a complex interaction between situational and personal variables (Carver, Scheier, & Weintraub, 1989).

RISK FACTORS FOR EMOTIONAL AND BEHAVIORAL LATE EFFECTS

To date, there has not been a single identified predictor of emotional and behavioral outcomes. Despite the difficulty in deciphering complex interactions of risk factors, some studies have aimed to identify common factors associated with late effects in survivors. Most studies unfortunately, have aimed at investigating *cognitive* late effects and have not thoroughly aimed to advance knowledge about which risk factors may be involved in the development of psychological and behavioral late effects in pediatric survivors. In addition, existing studies investigating late effects have predominantly focused on the effects of radiation in specific cancer populations (i.e. brain tumors; Fuemmeler, Elkin & Mullins, 2002; Mulhern, Hancock, Fairclough & Kun, 1992; Ris & Noll, 1994) and have not investigated specific, possible risk factors for negative psychological and behavioral late effects in child cancer survivors of ALL.

Intensity of Treatment

The well-documented negative sequelae of treatment for ALL has lead a few worldwide clinical-trial cooperative groups, (e.g. Children's Oncology Group, Dutch Childhood Leukemia Study Group) to adopt specific treatment protocols in order to reduce the negative impact on the CNS. Another one of these adopted procedures was the classification of risk. In 1993, the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) sponsored a meeting with representatives from the Children's Cancer Group (CCG), Pediatric Oncology Group (POG), Dana-Farber Cancer Institute (DFCI), and St. Jude Children's Research Hospital (SJCRH). At that meeting, it was determined that risk-based treatment was the best course in treating children with ALL. The low-risk group would consist of individuals ages 1-9, with a white blood count of 50,000/MicroL. The remaining patients would be classified as having high-risk ALL. The difference also being that the low-risk group had a 4-year Event Free Survival (EFS) rate of approximately 80%, with the high-risk group having an EFS of approximately 65% (Smith, et al., 1996). The classification risk from that point on thus impacted the intensity of treatment the individual would receive. Low-risk patients would receive standard chemotherapy treatment, while the high-risk patients received intensified treatment. Although there are differences in varying differences within clinical trials and the exact treatments used, the general consensus is that high-risk ALL patients are exposed to a higher cumulative systemic methotrexate dose (Buizer, et al., 2005).

Although the literature regarding chemotherapy-only treatment effects is limited, one study in particular showed that higher doses of CNS-chemotherapy led to attentional difficulties that were positively related to the intensity of chemotherapy treatment, with the intensified treatment group performing worse on measures of attentional flexibility,

sustained attention and visuo-motor control than the standard treatment group. The authors purported that the deficits observed are part of a larger deficit in executive functioning resulting from the intensified chemotherapy treatment. According to Buizer et al., (2005, pg. 286), "Executive functions are defined as those skills necessary for purposeful, goal-directed, controlled activity, and are generally considered to be largely mediated by the frontal and prefrontal cortices of the brain." The findings are consistent with previous literature suggesting that high intensity chemotherapy can result in deficits of attention, memory, visuospatial skills, executive function, and emotional status (Filley & Leinschmidt, 2001). Despite his findings, the literature remains largely absent of research investigating differences in *emotional and behavioral late effects* with regards to standard vs. high-risk treatments.

Age

Past research has demonstrated that the developmental level of the child at the time that diagnosis and treatment begins can have an impact on possible neurotoxic effects resulting from treatment. These effects may include damage to white matter, low cognitive functioning (and in some cases mental retardation), and lower scores on neuropsychological measures of verbal auditory memory, visual motor integration and fine motor functioning (Davis, Hoffman, Pearl & Braun, 1986; Duffner et al., 1993; Duffner, Cohen, Myers & Heise, 1986; Evans, Jenkins & Sposto, 1990). However, how these physiological changes lead to psychological and behavioral sequelae is less understood.

Additionally, much of the literature focusing on age and its association with the development of psychological and behavioral late-effects has focused on adolescents; a period of time when major biochemical and physiological changes occur in humans (Hamburg, Takinishi, 1989). During this time, the adolescent also teeters between

childhood and adulthood and begins to struggle with questions regarding independence, emotional and physical maturity and development of sex-role identity. Additionally, today's adolescents face an ever-increasing lack of family and social support due to the increase in geographic mobility, widespread extended families and single-parent households. The pervasiveness of drugs, violence and other health-damaging behaviors in current western culture serves to compound the already difficult challenge of transitioning into adulthood (Hamburg, Takinishi, 1989). Adding a life-threatening disease like cancer to this existing web of stressors causes it to become clear that adolescents' "Coping threshold is threatened and development through the adolescent stages may be compromised" (Anderson & Arnold, 1998, pg. 121).

Lansky et al. (1986) was one of the first to suggest that developmental disruptions due to cancer can lead to elevated risks of developing psychological problems when individuals are diagnosed in adolescence (compared to those diagnosed in early childhood). The investigators suggest that this is due, in part, to the already stressful adolescent period. Adding a diagnosis of cancer during this time may have an impact on peer relationships, may cause isolation from school and peers (due to frequent hospitalizations), may force them to confront the realities about future school and occupational goals (due to possible declines in cognitive abilities, physical limitations resulting from their cancer and treatment, etc.) and may bring to the forefront questions about possible sexual and future reproductive dysfunction (due to intensive treatment protocols). Similarly, others have demonstrated that individuals who were diagnosed and treated at an early age had subsequently less psychosocial difficulty than those who were diagnosed in adolescence. The researchers postulate that perhaps the more time that has passed since diagnosis and treatment, the less anxiety may be felt about recurrence of the disease (Koocher O'Malley, Gogan & Foster 1980).

Other studies have come to differing conclusions. Fritz and Williams (1998), demonstrated that illness-related variables like age were not associated with psychological and social adjustment later in life to any significant degree. Another investigation postulated that adolescents would have *better* psychosocial outcomes post-treatment because stressful experiences like being diagnosed with cancer allow adolescents the opportunity to practice, utilize and alter coping strategies in order to reduce anxiety leading to greater and longer-lasting positive self-concept. Results from this study indicated that adolescents did not exhibit overt psychological problems due to cancer or its treatment, had more extensive and effective coping strategies and had adequate self-concept and self-esteem. Because avoidance behavior has been documented in the literature for childhood survivors of cancer (particularly with literature linking childhood cancer and PTSD symptoms), these investigators postulated that adolescent cancer survivors maintained adequate self-concept and self-esteem by avoiding any factor that would threaten their view (Bauld et al., 1998) Anderson & Arnold, 1998). However, despite adequate self-concept and self-esteem in adolescents, the investigators discovered that older adolescent survivors (15-17) were still more prone to worry than younger adolescents (12-14).

Some studies have demonstrated that the development of the child could play a significant role in the resulting severity of neurotoxic effects of treatment, with younger children more susceptible to treatment-related neurotoxicity such as toxic leukoencephalopathy (Davis, Hoffman, Pearl & Braun, 1986). Researchers suspect that cognitive late effects are in part, affected by treatments which negatively impact the development of the central nervous system (such as interference and reduction in the production of white matter) is most vulnerable to insult in younger children (Armstrong & Mulhern, 1999), possibly increasing the chance of experiencing deficits in attention,

inhibition, organized planning and initiation, memory, processing speed, changes in personality, depression, and anxiety.

Gender

Investigations into gender-specific risk factors for increased neurotoxicity related to treatment for ALL are mostly limited to populations that have undergone cranial radiation therapy. These investigations indicate that women and girls are at a significantly greater risk for developing cognitive late effects than males. A study by Waber, Tarbell, Kahn, Gelber and Sallan (1992) investigated neuropsychological outcomes in children with ALL. Participants in this study were between the ages of 6-16 and were all in continuous remission (i.e. participants were tested an average of 77 months after initial diagnosis). Patients had been randomized to receive either low-dose intrathecal (IT) methotrexate treatment (MTX) with 1,800-cGy CRT or high-dose IT MTX with 2,800-cGy CRT. Females who received a single high dose of IV MTX were associated with lower general cognitive performance (i.e. I.Q.); however, this effect was not significant for males. Although males exhibited some decline in language-based academic skills, their profile was more consistent with individuals who have language/learning disabilities while females' late effects manifested as global depression of cognitive functioning (Waber et al., 1992).

Another study demonstrated that chemotherapy-only treatment led to lower overall global intelligence and declines in verbal skills for females (Von der Weid, Mosimann, Hirt et al., 2003). Similarly, another investigation reported that females were more susceptible to lower scores on measures of attention and information processing when compared to males; although, the investigators note that males performed worse on measures of sustained attention. Coinciding with previous research that has shown developmental differences in the mass of white matter found in developing brains (with

females having less white matter than males), the researchers purport that perhaps the smaller amount of white matter in females leaves the brain more susceptible to "neurotoxic insult" (Buizer, de Sonneville, van den Heuvel – Eibrink, & Veerman, 2005).

Unfortunately, the literature is absent on genders effect for emotional and behavioral functioning post-treatment; however, because females may be more susceptible to toxicity from treatment, they may also more likely to sustain white matter damage. As was noted earlier, white matter damage may lead to deficits in executive functioning, including problems organizing, planning and initiating goal-directed activity; therefore, females may be more prone to experience behavioral problems due to a decrease in inhibitory control and personality changes (e.g. increased irritability, aggression, apathy, etc.; Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000).

STATEMENT OF THE PROBLEM

The most common form of childhood cancer is Acute Lymphoblastic Leukemia (ALL) (Waber & Mullenix, 2000; Ries, Miller & Hankey, 1994). Children with ALL can expect to be treated with one, or a combination of the following: systemic chemotherapy (i.e. chemotherapy introduced orally, injected into veins and/or muscles) and Central Nervous System (CNS) chemotherapy; in more extreme, high-risk cases, when leukemic cells have spread throughout organs and/or the brain and spinal cord, radiation therapy and/or or bone-marrow transplantation may be used (Daly et al., 2008).

The increased chance of survival of pediatric cancer patients in recent years poses a varied spectrum of challenges for patients and their families; Patients treated for ALL may experience short- and long-term physiological effects due to treatment. In addition, because pediatric patients are given much higher doses of chemotherapy and radiation than was common a few years ago (Noll et al., 1999), they may be more susceptible to neurotoxic insult and inadvertent white matter damage to the brain. One of the few

studies to investigate the effects of CNS-directed chemotherapy discovered that more intense treatment positively correlated with increased attentional difficulties (specifically resulting in problems with attentional flexibility, sustained attention) and visuo-motor control (Buizer et al., 2005). Another investigation found similar effects, with more high-intensity chemotherapy resulting in deficits of attention, memory, visuospatial skills, executive function, and emotional status (Filley & Leinschmidt, 2001). Despite these findings, pediatric patients with more aggressive leukemia (e.g. having leukemic cells migrate to organ systems, and into the brain and spinal cord) continue to be routinely exposed to high-intensity treatment protocols such as combination treatment protocols (i.e. chemotherapy plus radiation) that act on the CNS. This method of treatment delivery often leaves children and adolescents vulnerable to neurotoxic injury and longer lasting neuropsychological, neurocognitive and cognitive late effects. Less understood, however, is whether treatment and the traumatic experience of battling a life-threatening illness leads to long-term *emotional* and *behavioral* maladjustment for pediatric oncology survivors.

Studies investigating pediatric survivors have demonstrated that negative emotional and behavioral late effects can and do occur (Hobbie et al., 2000; Buizer et al. 2006; Novakovic et al., 1996; Mulhern, Wasserman, Friedman, & Fairclough, 1989), and it has been purported that survivors experience higher rates of depression, anxiety and low self-esteem (Koocher, O'Malley, Gogan, & Foster, 1980; Kazak, 1994). Anxiety in particular, has been identified as one of the longest lasting psychological sequelae of cancer (Kazak, 1994). Still, the data on long-term psychological sequelae is mixed, with some studies even suggesting healthy, long-term, psychological adjustment (Brown et al., 1992; Fritz, Williams & Amylon, 1988; Greenberg, Kazak, & Meadows, 1989).

Behavioral effects of cancer in pediatric patients are not well understood. Some studies have reported excessive behavioral problems occurring in pediatric ALL patients undergoing radiation treatment; however, others have concluded that pediatric patients are considered by their peers to be less aggressive and enjoy healthy interpersonal relationships with classmates when compared to normative peers (Noll, et al, 1999). Despite the varying reports, the most common behavioral deficits reported to occur in pediatric survivors are problems with attention. Some researchers suggest that attentional difficulties are a direct result of white matter damage caused by high-intensity chemotherapy targeting the brain and spinal cord (Buizer, de Sonneville, PhD, van den Heuvel – Eibrink, & Veerman, 2005). White matter damage is thought to lead to deficits in executive function. Because executive function is important for purposeful, goal-directed activity, damage to this area can result in behavioral problems due to a decrease in inhibitory control and personality changes (e.g. increased irritability, aggression, apathy, etc.; Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000).

The intensity of treatment is a risk factor that can determine the severity of emotional and behavioral adjustment in pediatric oncology survivors. Little is known about other possible characteristics that may make it more likely for a survivor to develop emotional and behavioral problems. For example, it has been suggested that the age of the pediatric patient at the time of diagnosis and treatment is an important risk factor in the development of emotional and behavioral late effects. However, the literature is mixed regarding age and its effect, with some concluding that younger individuals fare better (Compas, Banez, Malcarne & Worsham, 1991) while others reporting the opposite (Pelcovitz et al., 1998; Burgess, 1985; Kulka et al., 1990; van der Kolk, 1985; Lansky et al. 1986). Similarly, some have concluded that older children fare better in the long run because they are developmentally more mature and better equipped with coping

strategies to help reduce distress. Gender has also been identified as another potential risk factor; however, unlike age, gender has been implicated in affecting cognition while the effect of sex on emotional and behavioral outcomes has not been thoroughly investigated. (Von der Weid, Mosimann, Hirt et al., 2003).

Although there has been some research done in this field, overall research in this field is limited. Thus, this investigation will be considered a pilot study to determine the feasibility and perhaps improve upon the design of the research. The purpose of this pilot study was thus to investigate emotional (depression and anxiety) and behavioral (attention and hyperactivity) late effects for ALL diagnosis and treatment in pediatric oncology survivors, as well as to investigate potential risk factors (such as gender, age that treatment was started, and treatment intensity) that may make it more likely to develop emotional and behavioral late effects. In researching late effects and the impact of certain risk-factors, this investigation hoped to provide useful information that could inform the development of differentiated psychosocial care protocols involving parents, teachers and surrounding communities, as well as to prevent (or lessen the impact of) and improve long-term emotional and behavioral outcomes for pediatric survivors of ALL.

CHAPTER III: METHOD

PROJECT APPROVAL

The proposed study complied with the ethical issues and standards of research delineated by the American Psychological Association (2002) and the Procedures Governing Research with Human Subjects at Dell Children's Medical Center of Central Texas (Austin, TX). Approval for this study was received by: the Departmental Review Committee in the Department of Educational Psychology, the Institutional Review Board (IRB) of The University of Texas at Austin, the Brackenridge Hospital IRB and the Clinical Research Steering Committee (CRSC) at Seton Hospital, Austin TX.

PROCEDURE

Emotional and behavioral assessment was conducted using the Behavioral Assessment Scale for Children, Second Edition (BASC-2). Data was collected in two different ways, from a) participants and b) through archival data.

Data Collection Procedure #1

Participants for this study were identified through the LIVESTRONG Survivorship Clinic at Dell Children's Hospital, Austin, TX. A flyer was included as part of the LIVESTRONG checkup protocol that patients and families received during their annual survivor checkups. (An e-mail version of this flyer was also sent out to a listserv of LIVESTRONG patients and their families.) The flyer and e-mail included a brief description of the study and asked families of survivors to indicate their interest in receiving additional information about the study. The flyer and e-mail also asked that those who were interested include their name, address, and child's age (to determine which age-appropriate assent forms to send).

As the primary investigator received signed flyers indicating families' consent to receive more information, the survivor and primary caregiver were mailed an initial packet that included: a) an Informed Consent letter (Appendix A) explaining the purpose and nature of this investigation, as well as information about confidentiality and any risks associated with participation in this study. This packet also included b) Parental Informed Consent form (Appendix B), Student Assent form (Appendix C), and Demographic form (Appendix D). The identified participant and their primary caregiver were asked to return all forms in a self-addressed stamped envelope that was provided by the investigator. *All forms provided were either in English or Spanish versions*.

Only those participants who returned signed consent forms were allowed to participate in this investigation. Those giving consent to participate were mailed a second packet of materials to complete. The packet included: a) appropriate BASC-2 Self Report of Personality (SRP) form for the child or adolescent participant; and b) Parent Rating Scales (PRS) form for the child's primary caregiver. The participants were asked to complete all forms and return all completed materials in a self-addressed stamped envelope that was provided by the investigator. Only two families agreed to participate via this method.

Data Collection Procedure #2

Archival (existing) data was also used for this study. The archival data used in *this* study was collected as part of a neuropsychological test battery administered to Acute Lymphoblastic Leukemia (ALL) child survivors at the LIVESTRONG Survivorship Center in Austin, TX. Only data from those participants who consented for their information to be used in other research was included in *this* study. The data used came from the BASC-2 Parent AND Self-Report measures. No personally identifying

information was used except for demographic data if available. Data for eighteen survivors and fifteen caregivers were collected in this manner.

PARTICIPANTS

This study included 20 ALL survivors and 17 caregivers. Two participants and two caregivers were recruited through flyers included with their annual LIVESTRONG checkup protocol; archival data was used for eighteen survivors and fifteen caregivers. Fifteen survivors were male and five were female. Fifteen were identified as Caucasian and five as Hispanic. The survivors ranged in age from 120 months (10 years), to 262 months (21.8 years) at the time of assessment. Children and adolescents who participated in this investigation met the following criteria: participants were treated with chemotherapy only; treatment had been completed for a minimum of one-year at the time of assessment. Exclusionary criteria applied. Participants who were currently undergoing treatment for ALL were not included in this investigation, as well as those who underwent a bone-marrow transplant, or had a recurrence of ALL, or other form of cancer. Two of the caregivers were biological mothers of survivors; the demographics for other caregivers were unknown.

INSTRUMENTATION

The Behavioral Assessment System for Children – Second Edition (BASC-2). The BASC-2 (Reynolds & Kamphaus, 2004) is a revision of the original Behavioral Assessment System for Children (BASC; Reynolds & Kamphaus, 1992). The BASC-2 is a "multimethod, multidimensional system used to evaluate the behavior and self-perceptions of children and young adults aged 2 through 25 years" (Reynolds & Kamphaus, 2004). The BASC-2 contains certain advantages over other behavioral and emotional assessment measures. For example, it only requires a 4th grade reading level, it

is available in English and Spanish forms, and includes an audio component for parents with reading difficulties.

Specifically, the BASC-2 assesses certain characteristics of behavior, both *adaptive and maladaptive,* and statistics performed on the measure indicate it is a reliable gauge of the emotional functioning of children and adolescents. The BASC-2 rating system can be used to differentiate emotional and behavioral disorders in children as well as to facilitate the development of appropriate treatment plans. It can be used individually, or in combinations of child, parent and teacher forms. The Parent Rating Scale (PRS) gathers information regarding a child's observable behavior. The PRS measures adaptive skills such as whether or not the child in question makes friends easily, etc., and provides an assessment of emotion and behavior. The second form used, a Self-Report of Personality (SRP), assesses the child's own emotions and self-perceptions. (There is also a teacher rating form, but it was not used in this study).

The PRS is divided into three age-appropriate forms: the preschool form for ages 2-5, the interview and child form for ages 6-11, and the adolescent form for ages 12-21. The PRS form contains Likert responses: *Never, Sometimes, Often* and *Almost Always* producing 4-5 broad Composite Scales. These include: *Internalizing Problems, Externalizing Problems, Adaptive Skills and a Behavioral Symptoms Index*. The Internalizing Composite is made up of Anxiety, Depression and Somatization scales. The Externalizing Composite is made up of Hyperactivity, Aggression, and Conduct Problems scales. The Behavioral Symptoms Index is made up of Hyperactivity, Aggression, Depression, Attention Problems, Atypicality, and Withdrawal scales. The PRS form provides optional Content Scales in the areas of Anger Control, Bullying, Developmental Social Disorders, Emotional Self-Control, Executive Functioning,

Negative Emotionality, and Resiliency that can help distinguish between social maladjustment and emotional disturbance (Reynolds and Kamphaus, 2004).

The SRP consists of four different forms for children ages 6-7 and 8-11, adolescents aged 12-18 and college individuals aged 18-25. The SRP form contains items in both True/False format and 4-point Likert responses like those on the PRS form. The child and adolescent forms used in this study produce identical Composite Scales: *Emotional Symptoms Index (ESI), Internalizing Problems, Inattention/Hyperactivity, Personal Adjustment and School Problems*. The ESI is a composite score for Social Stress, Anxiety, Depression, Sense of Inadequacy, Self-Esteem and Self-Reliance. The Internalizing Composite results from scores on Atypicality, Locus of Control, Social Stress, Anxiety, Depression, Sense of Inadequacy, and Somatization scales. The Inattention/Hyperactivity Composite Scale is made up of Attention Problems and Hyperactivity scales. The Personal Adjustment Composite is made up of scales for Relations with Parents, Interpersonal Relations, Self-Esteem and Self-Reliance. The School Problems Composite is made up of scales that include Attitude to School, Attitude to Teachers and Sensation Seeking (adolescent form only) (Reynolds & Kamphaus, 2004).

Administration time varies between 10-20 minutes for the PRS form, and 20-30 minutes for the SRP form. The PRS and SRP can be scored by hand, by manual entry into the computer and/or scantron (Reynolds & Kamphaus, 2004). The PRS and SRP forms contain validity indexes. The F-Index (faking bad) is included in all forms; the SRP includes an additional L-Index (faking good), which purportedly measures an individual's level of positive bias. The SRP also includes a V index which uses "nonsensical statements" in order to measure the validity of individual's responding to test items. The PRS also includeS two additional validity scores: the Consistency Index

is sensitive to random responses and the Response Pattern Index is sensitive to invalid responses due to a respondent's lack of attentiveness to test items (Reynolds & Kamphaus, 2004).

According to Reynolds and Kamphaus (2004), the BASC-2 was normed using both general and clinical samples. General norms were based on the *2001 Current Population Survey* in regards to gender, socioeconomic status (as indicated by mother's education level), race/ethnicity, geographic location, and special education classification. Participants included 4,800 for the PRS form and 3,400 for the SRP form. The author's also normed the BASC-2 on a clinical population whose sample sizes were as follows: 1,975 for the PRS form; and 1,527 for the SRP form. Approximately 100 participants represented each age level, except for 6- and 18-year-olds.

Both English and Spanish forms were utilized depending on the rater's language proficiency. The child PRS contains 160 items; the adolescent PRS contains 150 items; the child SRP contains 139 items; the adolescent SRP contains 176 items. Answers for each form were bubbled onto a protocol, which was then entered manually into the BASC-2 computer-scoring program.

The BASC-2 has been demonstrated to have high acceptable internal consistency; with correlations generally falling into the .90 range for Composite scales and in the mid .80 range for individual scales across forms (PRS and SRP) and normative samples (general and clinical). The PRS Composites have an internal consistency of .95 for 8-11 year olds, .95 for 12-14 year olds, and .93 for 15-18 year olds. Internal consistency scores for SRP Composites range from .88 for 8-11 year-olds, .90 for 12-14 year-olds and .89 for 15-18 year-olds. PRS scales internal consistency is .86 for 8-11 year-olds, and .85 for 12-18 year-olds. SRP scales internal consistency is .80 for 8-11 year-olds, .82 for 12-14 year-olds and .79 for 15-18 year-olds. (Reynolds & Kamphaus, 2004).

Test-retest reliability for the PRS and SRP forms yielded average correlations in the .80 range for Composite scores and between .70-.80 for individual scales across all age groups. Interrater reliability is considerably lower with median reliabilities for Composite scores (across teacher and parent forms) ranging from .54 to .74. Median coefficients across individual scales ranged from .53-.65 for TRS samples. PRS forms have reliability coefficients in the mid .70 range across Composite and scale scores (Reynolds & Kamphaus, 2004). The BASC-2 provides T-scores for both individual scales and Composite scores on all rating forms. T-scores and percentiles can be calculated using general population and/or combined-sex norms, or by selected clinical population and/or separate-sex norms. Higher T-scores are indicative of pathology on all forms, except for the Adaptive Skills Composite (for parents and teacher forms) and Personal Adjustment Composite (for child and adolescents forms), where lower T-scores are suggestive of pathology. Specifically, scores are reported as T-scores with a mean of 50 and standard deviation of 10. Among the clinical scales, scores of 60 through 69 are considered at risk and scores of 70 and above are considered clinically significant. With adaptive scales, scores of 31 through 40 are considered at-risk whereas scores of 30 and below are considered clinically significant.

As of present, few studies have investigated the emotional and behavioral outcomes/late effects in child survivors of cancer. The few that have investigated such factors have done so using the Child Behavior Checklist (CBCL; Liang et al., 2006; Mulhern et al., 1989). The CBCL can be used to measure social and behavioral problems; however, unlike the BASC-2, it does not identify variability in various domains within the range of normal childhood behavior. In order to most adequately assess emotional and behavioral functioning, it would be helpful for the measure to address both negative and positive aspects of functioning; although this study primarily aims to investigate

emotional and behavioral late effects, measures that also assess positive aspects of functioning can provide important information regarding potential protective factors. Extant investigations using the BASC-2 for cancer patients are limited; however, it has been utilized in some studies involving ALL patients (Challinor, 1998; Shelby, Nagle, Barnett-Gueen, Quattlebaum, & Wuori, 1998; Shelby, 1999). Despite this limitation, the BASC-2 is believed to be an appropriate instrument for this population because it measures both positive and negative aspects of emotional and behavioral functioning, it allows for comparison between respondents and general and/or clinical normative populations, it provides investigators the opportunity to use combined- and/or separate-sex norms and it is available in both English and Spanish.

Demographic Intake Form. Two primary caregivers were asked to complete a demographic form which included questions about the child's age and gender, length of time since diagnosis, length of time since illness, type of cancer, treatment received, race/ethnicity, occupation, educational and marital status. No other participants completed the demographic form because all other data was archival.

RESEARCH QUESTIONS, HYPOTHESES AND DATA ANALYSIS

Question 1

Are there significant mean differences in emotional (depression and anxiety) and behavioral functioning (attention and hyperactivity) reported between males and female pediatric survivors of ALL?

Hypothesis 1. It was hypothesized that significant gender differences would be present. Girls would report significantly more emotional/internalizing (i.e. anxiety, depression) and behavioral/externalizing (hyperactivity attention problems) problems than males.

Rationale

Studies have shown that females exhibited more global depression of cognitive functioning and exhibit lower verbal skills when compared to males (Waber et al., 1992; Von der Weid, Mosimann, Hirt et al., 2003). Females have also been shown to perform worse on measures of attention and information processing when compared to males (Von der Weid, Mosimann, Hirt et al., 2003). Researchers purport that perhaps the smaller amount of white matter in females leaves the brain more susceptible to "neurotoxic insult" (Buizer, de Sonneville, PhD, van den Heuvel–Eibrink, & Veerman, 2005). If this is the case and females are more susceptible to white matter damage, we would expect to see deficits in executive functioning. Because executive functions are necessary for "purposeful, goal-directed, controlled activity," any damage to the area of the brain responsible for this behavior may result in emotional and behavioral problems, especially in the areas of attention. Supporting this point further is research that has made associations between damage to white matter and problems with attention, cognition, emotions and personality changes (Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000). Specifically, Filley & Leinschmidt (2001) propose that personality and emotional changes, such as apathy, depression and anxiety, are common symptoms of white matter damage.

Question 2

Are there significant mean differences in the reporting of emotional and behavioral problems between differing treatment groups (low-intensity vs high-intensity chemotherapy) for pediatric survivors of ALL?

Hypothesis 2. It was hypothesized that significant group differences are present. It was expected that those undergoing high intensity treatment would report more

difficulty with hyperactivity, and attention due to inadvertent damage to white matter (Buizer, et al., 2005).

Rationale

Buizer et al., (2005) demonstrated that CNS-directed chemotherapy led to attentional difficulties that was positively related to the intensity of chemotherapy treatment – with the intensified treatment group performing worse on measures of attentional flexibility, sustained attention and visuo-motor control than the standard treatment group. The authors purport that the deficits observed are part of a larger deficit in executive functioning that resulted from the intensified chemotherapy treatment. Because white matter damage has been linked to deficits in executive functions, (Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000) and because executive functions are necessary for inhibitory control, any damage to the area of the brain responsible for this behavior may also result in problems with attention and hyperactivity/impulsivity.

Question 3

Are there significant mean differences in the reporting of emotional and behavioral problems between differing age groups (0-4, 5-8, ≥9) at time that treatment began for pediatric survivors of ALL.

Hypothesis 3. It was hypothesized that significant group differences would be present. Those survivors who began treatment at an earlier age would report significantly more emotional/internalizing (anxiety and depression) and behavioral/externalizing (hyperactivity and attention) problems than those who started treatment at an older age.

Rationale

Age is a risk factor that has been purported to increase the risk for developing problematic neuropsychological and psychological late effects. Neurologically, the

developing brain is more susceptible to irreversible neurotoxic insult than older children and adolescents (Buizer et al., 2005). Exposing a younger brain to neurotoxic chemicals like chemotherapy can therefore more easily damage white matter and lead to executive functioning deficits.

One particular study hypothesized that adolescents might have better psychosocial outcomes, post-treatment, because life-threatening illnesses force them to practice, utilize and alter their coping strategies in order to reduce anxiety. Instead, the investigators concluded the opposite; their investigation demonstrated that older adolescent survivors (aged 15-17) worried more than those who were 12-14 years old. Despite this finding, adolescents did not exhibit overt psychological problems due to cancer or its treatment, had more extensive and effective coping strategies and had adequate self-concept and self-esteem (Bauld et al., 1998). Because 'avoidant' behaviors have been previously identified to occur in pediatric survivors of cancer, the authors purport that adolescents learn to avoid any reminders of their experience that may threaten their positive sense of self.

Additionally, an individual's coping style and coping efforts (i.e. cognitive or behavioral actions in order to reduce stress) can also determine the level of adjustment that is made in response to stress (Compas, 1987a). Because younger children have not typically navigated and developed emotion-based coping strategies at the level that older children and adolescents have, we would expect younger children to have a harder time finding ways to cope with their stressful experience (Lazarus, 1984). Coupled with neurotoxic exposure of chemotherapy in young children's developing brain (increasing their chance for white matter damage), it is hypothesized that younger children will be more prone to developing emotional and behavioral late effects.

Question 4

Are there significant mean differences in emotional (depression and anxiety) and behavioral functioning (attention and hyperactivity) as reported by caregivers, based on gender?

Hypothesis 4. It was hypothesized that significant gender differences would be present. Caregivers would report significantly more emotional/internalizing (i.e. anxiety, depression) and behavioral/externalizing (hyperactivity attention problems) problems for females.

Rationale

Studies have shown that females exhibited more global depression of cognitive functioning and exhibit lower verbal skills when compared to males (Waber et al., 1992; Von der Weid, Mosimann, Hirt et al., 2003). Females have also been shown to perform worse on measures of attention and information processing when compared to males (Von der Weid, Mosimann, Hirt et al., 2003). Researchers purport that perhaps the smaller amount of white matter in females leaves the brain more susceptible to "neurotoxic insult" (Buizer, de Sonneville, PhD, van den Heuvel–Eibrink, & Veerman, 2005). If this is the case and females are more susceptible to white matter damage, we would expect to see deficits in executive functioning. Because executive functions are necessary for "purposeful, goal-directed, controlled activity," any damage to the area of the brain responsible for this behavior may result in emotional and behavioral problems, especially in the areas of attention. Supporting this point further is research that has made associations between damage to white matter and problems with attention, cognition, emotions and personality changes (Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000). Specifically, Filley & Leinschmidt (2001) propose that personality and

emotional changes, such as apathy, depression and anxiety, are common symptoms of white matter damage.

Question 5

Are there significant mean differences in caregiver's reporting of emotional and behavioral problems between differing treatment groups (low-intensity vs. high-intensity chemotherapy) for pediatric survivors of ALL?

Hypothesis 5. It was hypothesized that significant group differences are present. It was expected that caregivers would report more problems with attention and hyperactivity for those undergoing high intensity treatment due to inadvertent damage to white matter (Buizer, et al., 2005).

Rationale

Buizer et al., (2005) demonstrated that CNS-directed chemotherapy led to attentional difficulties that was positively related to the intensity of chemotherapy treatment – with the intensified treatment group performing worse on measures of attentional flexibility, sustained attention and visuo-motor control than the standard treatment group. The authors purport that the deficits observed are part of a larger deficit in executive functioning that resulted from the intensified chemotherapy treatment. Because white matter damage has been linked to deficits in executive functions, (Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000) and because executive functions are necessary for inhibitory control, any damage to the area of the brain responsible for this behavior may also result in problems with attention and hyperactivity/impulsivity.

Question 6

Are there significant mean differences in caregivers' reporting of emotional and behavioral problems between differing age groups (0-4, 5-8, ≥9) at time that treatment began for pediatric survivors of ALL.

Hypothesis 6. It was hypothesized that significant group differences would be present. Caregivers would report more emotional/internalizing (anxiety and depression) and behavioral/externalizing (hyperactivity and attention problems) problems for those that started treatment at an earlier age than those who started treatment when they were older.

Rationale

Age is a risk factor that has been purported to increase the risk for developing problematic neuropsychological and psychological late effects. Neurologically, the developing brain is more susceptible to irreversible neurotoxic insult than older children and adolescents (Buizer et al., 2005). Exposing a younger brain to neurotoxic chemicals like chemotherapy can therefore more easily damage white matter and lead to executive functioning deficits.

One particular study hypothesized that adolescents might have better psychosocial outcomes, post-treatment, because life-threatening illnesses force them to practice, utilize and alter their coping strategies in order to reduce anxiety. Instead, the investigators concluded the opposite; their investigation demonstrated that older adolescent survivors (aged 15-17) worried more than those who were 12-14 years old. Despite this finding, adolescents did not exhibit overt psychological problems due to cancer or its treatment, had more extensive and effective coping strategies and had adequate self-concept and self-esteem (Bauld et al., 1998). Because 'avoidant' behaviors have been previously identified to occur in pediatric survivors of cancer, the authors purport that adolescents

learn to avoid any reminders of their experience that may threaten their positive sense of self.

Additionally, an individual's coping style and coping efforts (i.e. cognitive or behavioral actions in order to reduce stress) can also determine the level of adjustment that is made in response to stress (Compas, 1987a). Because younger children have not typically navigated and developed emotion-based coping strategies at the level that older children and adolescents have, we would expect younger children to have a harder time finding ways to cope with their stressful experience (Lazarus, 1984). Coupled with neurotoxic exposure of chemotherapy in young children's developing brain (increasing their chance for white matter damage), it is hypothesized that younger children will be more prone to developing emotional and behavioral late effects.

Question 7

Do survivors and caregivers significantly differ in their report of emotional (depression and anxiety) and behavioral functioning (attention and hyperactivity) in pediatric survivors of ALL?

Hypothesis 7. It was hypothesized that caregivers and survivors would significantly differ in their report of emotional and behavioral functioning. Caregivers would report more externalizing problems (attention and hyperactivity) because problems with hyperactivity and attention are inherently more observable.

Rationale

There exists some conflict in the literature regarding the correlation of cross reporting between different informants on measures of internalizing and externalizing behavior. However, there is general agreement that parents tend to report more difficulty with externalizing problems than internalizing problems, which are by nature less

observable (Deng, Liu, Roosa, 2004). Thus, we would expect that parents and survivors would differ in their report of externalizing problems.

CHAPTER IV: RESULTS

This chapter presents the statistical analysis for this *pilot* study. Although there has been some research investigating psychological outcomes in survivors of Acute Lymphoblastic Leukemia (ALL), overall research in this field is limited and there has not been a clearly defined methodology for addressing these variables in this population. Thus, this investigation will be considered a pilot study to determine the feasibility and contribute to improving upon the design of this research. First, descriptive statistics are used to describe and summarize the data collected. Next, primary results are provided for each research hypothesis. Finally, exploratory analysis is presented in order to examine additional factors (late effects) that appear to be positive and adaptive in nature.

DESCRIPTIVE ANALYSIS

This study included a total of twenty pediatric participants and seventeen caregivers. There were significantly more males than females (Table 1). Fifteen pediatric participants were male (75 %), and five were female (25%). However, this is consistent with the typical gender distribution for leukemia (Leukemia and Lymphoma Society, 2010). Fifteen pediatric participants were identified as Caucasian and five as Hispanic. The pediatric participants ranged in age between 120 months (10 years) and 262 months (21.8 years) (Table 2). The age range when participants began treatment was between 18 months (1.5 years) and 138 months (11.5 years). Thirteen (65%) of the pediatric participants were considered 'low-risk' at their time of diagnosis and thus received low-intensity chemotherapy (Table 3). Six (30%) individual pediatric participants were considered 'high-risk' and received high-intensity chemotherapy. One participant's risk-level was unknown.

Table 1: Gender

	Frequency	Percent
Male	15	75%
Female	5	25%
Total	20	

Table 2: Age in Months (Years)

	Minimum	Maximum	Mean	Std. Deviation
Assessment	120 (10 years)	262 (21.8 years)	179.65 (13.8 years)	39.862 (3.3 years)
Starting Treatment	18 (1.5 years)	138 (11.5 years)	65.75 (5.5 years)	35.430 (2.9 years)

Table 3: Chemotherapy Intensity

	Males	Females	Total	Percent
Low-Intensity	11	2	13	65%
High-Intensity	3	3	6	30%
Unknown	0	1	1	5%

PRELIMINARY ANALYSIS

Before formal analysis, missing BASC-2 data was analyzed and addressed. A total of three BASC-2 caregiver reports were missing. The missing caregiver data was replaced by using the "series mean" in the Statistical Package for the Social Sciences (SPSS) program which gave an output as a mean of all available cases for a specific variable. This was done to reach an N=20 (for caregivers) for the purpose of achieving 80% power. As Campbell et al. notes (2007), the vast majority of published research in the past 20 years that has investigated the late effects of chemotherapy in pediatric ALL survivors has included a mean sample size of 13 treatment participants and evidenced a medium effect size (Hedge's *g* ranging from 0.34 to 0.71) for neurocognitive late effects, when compared to healthy peer and sibling controls. While the present study did not include a true control group, a medium effect (i.e., 0.5 – 0.8; Cohen, 1992) when comparing performance to published norms was expected with a sample size of 20.

Additionally, Mertler and Vannatta (2005) note that "replacing 15% or less of a subject or variable will have little effect on the outcome of the analysis." The three missing parent-reports combined for an exact total of 15% missing for each dependent variable, allowing this study to replace missing data without significantly impacting the outcomes of this study's statistical analysis.

Outliers were next explored and defined for this study as any BASC t-score that was at least three standard deviations away from the mean. No outliers were present in this data set. Normality, linearity and homoscedasticity were also analyzed in order to meet the assumptions required for a MANOVA analysis. Due to the limited number of participants, tests indicated non-normality for many variables; however, MANOVA is fairly robust to this violation (Mertler & Vandatta, 2005). Tests of homoscedasticity or homogeneity of variance were analyzed and addressed using Box's Test. (Mertler & Vandatta, 2005).

Before primary analysis, a correlation matrix was created to determine whether the dependent variables (DV's) in this investigation correlated highly. According to Mertler and Vannatta (2005), MANOVA is suited to handle DV's that are moderately correlated, but does not handle highly correlated variables well. That is, if two dependent variables are highly correlated, it may *sometimes* be more beneficial to combine them into one, given the resulting loss in degrees of freedom if both are kept. Thus, an analysis of the correlation between DV's was appropriate.

The correlation matrix (Table 4) indicated numerous statistically significant correlations between variables. Within survivor's DV's, the highest correlation was between hyperactivity and attention (r=.68). Within caregiver DV's, notable correlations were observed between anxiety and depression (r=.73), and attention and hyperactivity (r=.78). As a general rule of thumb, any correlation above .70 is considered a high

correlation. Although there were high correlations observed in the correlation matrix (particularly the DV's for caregivers) it was determined that the DV's would not be combined. Specifically, combining those specific variables would make it difficult to discern the future direction of this research, in an already limited field of study. Additionally, discussion with others who may use this research indicated it would be more beneficial to analyze the DV's 'as is' in hopes that they would provide more specific understanding of the role that each DV plays in late effects of cancer survivors, while understanding degrees of freedom might be lost.

Table 4: Correlation Matrix for Survivor and Caregiver DV's

N=20		Anx (S)	Dep (S)	Att (S)	Hype (S)	Anx (P)	Dep (P)	Att (P)	Hype (P)
Anxiety (S)	r	1	**.673***	**.664***	.402	.435	**.727***	.372	.203
	sig		.001	.001	.079	.056	.000	.106	.390
Dep (S)	r	**.673***	1	**.593***	.175	.097	**.552***	**.554***	.230
	sig	.001		.006	.461	.684	.012	.011	.329
Attention (S)	r	**.664***	**.593***	1	**.683***	**.470***	**.739***	**.651***	**.640***
	sig	.001	.006		.001	.037	.000	.002	.002
Hype (S)	r	.402	.175	**.683***	1	**.632***	**.616***	.271	.372
	sig	.079	.461	.001		.003	.004	.248	.106
Anxiety (P)	r	.435	.097	**.470***	**.632***	1	**.733***	.339	.373
	sig	.056	.684	.037	.003		.000	.144	.105
Dep (P)	r	**.727***	**.552***	**.739***	**.616***	**.733***	1	**.619***	**.480***
	sig	.000	.012	.000	.004	.000		.004	.032
Attention (P)	r	.372	**.554***	**.651***	.271	.339	**.619***	1	**.789***
	sig	.106	.011	.002	.248	.144	.004		.000
Hype (P)	r	.203	.230	**.640***	.372	.373	**.480***	**.789***	1
	sig	.390	.329	.002	.106	.105	.032	.000	

s=survivor
p=caregiver

Seven one-way MANOVA's were conducted as part of this investigation: three separate one-way MANOVA's for survivors' self-report BASCS, three one-way MANOVA's for caregivers' BASCS, and one MANOVA combining both caregiver and

self-reports. ANOVA results are also presented (when appropriate). If significant results for the univariate ANOVA were found, Tukey's post hoc test was used to examine how groups differed. The Tukey post hoc method was chosen because it allows for comparisons between all possible pairs without being overly conservative, and while maintaining the experiment-wise error at the pre-established alpha level of 0.05 (Huck, 2004). All analyses were conducted using SPSS for Windows using an alpha level of 0.05.

ANALYSIS OF RESEARCH QUESTION 1

Research question 1 asked whether ALL survivors differed on BASC-2 emotional and behavioral scales based on gender. To examine survivor-reported differences between genders on the BASC-2, a MANOVA was conducted with gender as the independent variable (IV) and anxiety, depression, attention, and hyperactivity as the dependent variables (DV). These four DV's were chosen based on previous literature that indicates these deficits are common in cancer survivors (Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000; Koocher, O'Malley, Gogan, & Foster, 1980; Kazak, 1994). It was hypothesized that females would report significantly more emotional/internalizing (i.e. anxiety, depression) and behavioral/externalizing (hyperactivity, attention) problems than males. As described below, this hypothesis not supported by the data.

Means and standard deviations for the differences in gender are presented in Table 5. MANOVA results (Table 6) indicate the combined DV's do <u>not</u> vary significantly based on gender (Wilks' Λ=.091, $F(4, 15)=2.457$, $p=.091$, $n^2=.396$). The absence of a statistically significant main effect did not provide the needed support for the hypothesis, thus no further analysis were conducted. Results of the MANOVA do not provide support for our hypothesis that females report significantly more problems than males with regards to anxiety, depression, attention and hyperactivity.

Table 5: Means and standard deviations on self-report BASC-2 for Gender

	Gender	Mean (T-Score)	Std. Deviation	N
Anxiety	male	50.11	12.525	15
	female	55.00	11.068	5
	Total	51.33	12.087	20
Depression	male	50.51	15.897	15
	female	45.80	3.633	5
	Total	49.33	13.906	20
Attention	male	49.75	9.904	15
	female	57.20	10.663	5
	Total	51.61	10.352	20
Hyperactivity	male	48.75	5.782	15
	female	58.20	8.899	5
	Total	51.11	7.677	20

Table 6: Multivariate Analysis of Variance for Gender

Wilk's L	*F*	Hypothesis *df*	Error *df*	*p*	eta^2
.098	2.38	4	15	.098	.39

ANALYSIS OF RESEARCH QUESTION 2

Research question 2 asked whether ALL survivors differed on BASC-2 emotional and behavioral scales based on the intensity of chemotherapy they received. To examine survivor-reported differences between treatment intensity on the BASC-2, a MANOVA was conducted with treatment intensity as the IV and anxiety, depression, attention, and hyperactivity as the DV's. It was hypothesized that those undergoing high intensity treatment would report more difficulty with hyperactivity and attention due to inadvertent damage to white matter (Buizer, et al., 2005).

Means and standard deviations for differences based on treatment intensity are presented in Table 7. MANOVA results (Table 8) suggest that the combined DV's do not significantly vary based on treatment intensity (Wilks' Λ=.759, $F(4, 14)$=1.112,

p=.389, n^2=.241). The absence of a statistically significant main effect did not provide the needed support for the hypothesis, thus no further analysis were conducted. Results of the analysis did not provide support for the hypothesis that there are significant differences in attention and hyperactivity symptoms based on treatment intensity.

Table 7: Means and std. deviations on self-report BASC-2 for Intensity

	Intensity	Mean t-score	Std. Deviation	N
Anxiety	low	53.28	13.030	13
	high	48.33	10.783	6
	Total	51.72	12.291	19
Depression	low	52.90	16.064	13
	high	43.00	4.517	6
	Total	49.77	14.144	19
Attention	low	53.63	10.761	13
	high	46.83	9.496	6
	Total	51.49	10.620	19
Hyperactivity	low	50.48	7.558	13
	high	51.50	8.871	6
	Total	50.80	7.758	19

Table 8: Multivariate Analysis of Variance for Intensity

Wilk's L	*F*	Hypothesis *df*	Error *df*	*p*	eta^2
.759	1.112	4	14	.389	.241

ANALYSIS OF RESEARCH QUESTION 3

Research question 3 asked whether pediatric ALL survivors differed on BASC-2 emotional and behavioral scales based on the age when they started treatment; young (between 0-4 years), middle (between 5-8 years) and oldest (≥ 9 years). To examine survivor-reported differences based on this factor, a MANOVA was conducted across the following BASC-2 subscales: anxiety, depression, attention, and hyperactivity. It was hypothesized that individuals who started treatment earlier would report significantly

more difficulty with anxiety, depression, hyperactivity and attention, than those who started treatment later.

Means and standard deviations for differences based on age when treatment began are presented in Table 9. MANOVA results (Table 10) suggests that the DV's vary significantly based on the age when treatment was initiated (Wilks' Λ=.299, $F(8, 28)=2.898$, $p=.017$, $n^2=.453$). Following statistically significant MANOVA results, a one-way ANOVA was conducted for each dependent variable to further explore differences based on age when treatment was initiated. ANOVA results (Table 11) suggest that anxiety, depression, attention and hyperactivity do not differ significantly for age when treatment started. Results of the overall analysis provide support for the hypothesis that the combined DV's differ significantly based on the age when treatment was initiated; however, subsequent ANOVA results did not indicate any significance.

Table 9: Means and standard deviations on self-report BASC-2 for age at TX initiation

	Age	Mean t-score	Std. Deviation	N
Anxiety	young	50.76	13.742	11
	middle	56.56	9.736	6
	oldest	43.00	4.359	3
	Total	51.33	12.087	20
Depression	young	51.85	16.625	11
	middle	44.56	5.632	6
	oldest	49.67	16.503	3
	Total	49.33	13.906	20
Attention	young	54.24	11.731	11
	middle	50.27	7.186	6
	oldest	44.67	9.238	3
	Total	51.61	10.352	20
Hyperactivity	young	53.92	6.215	11
	middle	48.52	9.274	6
	oldest	46.00	7.000	3
	Total	51.11	7.677	20

Table 10: Multivariate Analysis of Variance for Age at TX Initiation

Wilk's L	*F*	Hypothesis *df*	Error *df*	*p*	eta^2
.299	2.898	8	28	**.017**	.453

Table 11: Univariate Analysis of Variance for Age at TX Initiation

	F	Hypothesis *df*	Error *df*	*p*	eta^2
Anxiety	1.330	2	17	.291	.135
Depression	.507	2	17	.611	.056
Attention	1.090	2	17	.359	.114
Hyperactivity	1.910	2	17	.179	.183

ANALYSIS OF RESEARCH QUESTION 4

Research question 4 asked whether caregiver report of emotional and behavioral functioning differed based on gender. To examine caregiver-reported differences, a MANOVA was conducted with gender as the IV and anxiety, depression, attention, and hyperactivity as the DV's. It was hypothesized that caregivers would report significantly more difficulty with anxiety, depression, hyperactivity, and attention in females than in males.

Means and standard deviations for caregiver-reported differences based on gender are presented in Table 12. MANOVA results (Table 13) suggest that the combined DV's do not significantly vary based on gender (Wilks' Λ=.681, $F(4, 15)$=1.760, p=.189, n^2=.319). The absence of a statistically significant main effect did not provide the needed support for the hypothesis, thus no further analysis were conducted. Results did not provide support for the hypothesis that gender differences were present based on parent-report.

Table 12: Means and standard deviations on BASC-2 parent-report for gender

	Gender	Mean t-score	Std. Deviation	N
Hyperactivity	male	50.90	9.075	15
	female	48.60	13.722	5
	Total	50.32	10.068	20
Anxiety	male	44.51	6.499	15
	female	52.60	11.739	5
	Total	46.53	8.548	20
Depression	male	51.04	10.386	15
	female	59.60	15.582	5
	Total	53.18	12.045	20
Attention Problems	male	54.11	11.544	15
	female	50.60	10.738	5
	Total	53.24	11.176	20

Table 13: Multivariate Analysis of Variance for Gender (Parent Report)

Wilk's L	*F*	Hypothesis *df*	Error *df*	*p*	eta^2
.681	1.760	4	15	.189	.319

ANALYSIS OF RESEARCH QUESTION 5

Research question 5 asked whether caregiver report of emotional and behavioral functioning differed based on intensity of treatment that survivors received. To examine caregiver-reported differences, a MANOVA was conducted with intensity as the IV and anxiety, depression, attention, and hyperactivity as the DV's. It was hypothesized that caregivers of children who received high intensity treatment would report more difficulty with attention and hyperactivity due to inadvertent white matter damage (Buizer, et al., 2006).

Means and standard deviations for parent-reported differences based on treatment intensity are presented in Table 14. MANOVA results (Table 15) suggest that the combined DV's do not significantly vary based on treatment intensity (Wilks' Λ=.749, $F(4, 14)=1.171$, $p=.365$, $n^2=.251$). The absence of a statistically significant main effect

did not provide the needed support for the hypothesis, thus no further analysis were conducted. Results did not provide support for the hypothesis that higher intensity treatment led to significantly more difficulty with emotional and behavioral functioning, as reported by caregivers.

Table 14: Means and std. deviations on BASC-2 parent-report for treatment intensity

	Intensity	Mean t-score	Std. Deviation	N
Hyperactivity	low	52.57	10.912	13
	high	44.17	5.382	6
	Total	49.92	10.176	19
Anxiety	low	47.28	8.750	13
	high	44.83	9.432	6
	Total	46.50	8.781	19
Depression	low	53.73	12.138	13
	high	52.17	13.977	6
	Total	53.24	12.372	19
Attention	low	56.52	11.455	13
	high	47.50	8.871	6
	Total	53.67	11.308	1

Table 15: Multivariate Analysis of Variance for Intensity of TX (Parent Report)

Wilk's L	*F*	Hypothesis *df*	Error *df*	*p*	eta^2
.749	1.171	4	14	.365	.251

ANALYSIS OF RESEARCH QUESTION 6

Research question 6 asked whether caregiver report of emotional and behavioral functioning differed based on age when treatment started. To examine caregiver-reported differences, a MANOVA was conducted with age of initiation as the IV and anxiety, depression, attention, and hyperactivity as the DV's. It was hypothesized that caregivers of children who started treatment earlier would report more difficulty with anxiety, depression, hyperactivity, and attention.

Means and standard deviations for parent-reported differences based on age when treatment started are presented in Table 16. MANOVA results (Table 17) suggest that the combined DV's do not differ significantly based on treatment intensity (Wilks' Λ=.749, $F(8, 28)$=, p=.813, n^2=.135). The absence of a statistically significant main effect did not provide the needed support for the hypothesis, thus no further analysis were conducted. Results did not provide support for the hypothesis that starting chemotherapy treatment at an earlier age leads to significantly more difficulty with emotional and behavioral functioning, as reported by caregivers.

Table 16: Means and std. deviations on BASC-2 parent-report for age at tx initiation

	Age	Mean t-score	Std. Deviation	N
Hyperactivity	young	53.55	12.193	11
	middle	48.41	3.432	6
	oldest	42.33	5.132	3
	Total	50.32	10.068	20
Anxiety	young	46.27	9.561	11
	middle	48.43	7.244	6
	oldest	43.67	9.074	3
	Total	46.53	8.548	20
Depression	young	53.36	13.764	11
	middle	53.75	8.254	6
	oldest	51.33	15.948	3
	Total	53.18	12.045	20
Attention	young	55.36	13.633	11
	middle	51.28	6.804	6
	oldest	49.33	9.074	3
	Total	53.24	11.176	20

Table 17: Multivariate Analysis of Variance for Age at TX Initiation (Parent Report)

Wilk's L	*F*	Hypothesis *df*	Error *df*	*p*	eta^2
.749	.545	8	28	.813	.135

ANALYSIS OF RESEARCH QUESTION 7

Research question 7 asked whether ALL survivors and their caregivers significantly differed in their report of problems with emotional and behavioral functioning. To examine differences between the two, a MANOVA was conducted with either survivor or caregiver as the IV and anxiety, depression, attention, and hyperactivity as the DV's. It was hypothesized that caregivers of child survivors would report more difficulty with anxiety, depression, hyperactivity, and attention.

Means and standard deviations for differences based on 'reporter-type' (survivor or caregiver) are presented in Table 18. MANOVA results (Table 19) suggest that the combined DV's do not differ significantly based on the type of reporter (survivor or caregiver); Wilks' Λ=.798, $F(4, 35)$=, p=.087, n^2=.202). The absence of a statistically significant main effect did not provide the needed support for the hypothesis, thus no further analysis were conducted. Results did not provide support for the hypothesis that caregivers or survivors differ significantly in their report of problems.

Table 18: Means and std. deviations for differences in reporting between reporters

	Reporter	Mean t-score	Std. Deviation	N
Depression	child	49.33	13.906	20
	parent	53.18	12.045	20
	Total	51.25	12.987	40
Anxiety	child	51.33	12.087	20
	parent	46.53	8.548	20
	Total	48.93	10.616	40
Attention	child	51.61	10.352	20
	parent	53.24	11.176	20
	Total	52.42	10.665	40
Hyperactivity	child	51.11	7.677	20
	parent	50.32	10.068	20
	Total	50.72	8.846	40

Table 19: Multivariate Analysis of Variance for Reporter-Type

Wilk's L	*F*	Hypothesis *df*	Error *df*	*p*	eta^2
.798	2.218	4	35	.087	.202

EXPLORATORY ANALYSIS

The primary focus of this study was to investigate the specific types of psychological late effects that survivors of cancer can experience months to years after treatment is completed. However, like most previous research, investigations such as this one often assume that all effects experienced are negative in nature, and fail to address potential positive outcomes. To explore potentially adaptive late effects, three separate MANOVA's were completed based on survivor reports. Independent variables studied in this investigation remained the same. Dependent variables that described positive adaptive functioning were chosen from the adaptive subscales from the BASC-2. They included: relations with parents, interpersonal relations, self-esteem and self-reliance. These adaptive scales were chosen based on research that suggests cancer survivors experience healthy long-term psychological adjustment (Brown et al., 1992; Fritz, Williams & Amylon, 1988; Greenberg, Kazak, & Meadows, 1989), have a more positive outlook, have higher motivation to interact with peers, exhibit investment in interpersonal relationships, (Novakovic, et al. 1996, Verrill et al. 2000) and experience greater social acceptance by peers (Noll, et al., 1999).

The first MANOVA was conducted using gender as the IV, and DV's of relations with parents, interpersonal relations, self-esteem, and self-reliance. Means and standard deviations for differences based on gender are presented in Table 20. MANOVA results (Table 21) suggest that the combined DV's do <u>not</u> differ significantly based on gender (Wilks' Λ=.588, $F(4, 315)$=, p=.076, n^2=.412). The absence of a statistically significant

main effect did not provide the needed support for the hypothesis, thus no further analysis were conducted.

Table 20: Means and std. deviations for differences in adaptive skills based on gender

	Gender	Mean t-score	Standard Deviation	N
Relations with Parents	male	52.45	9.404	15
	female	50.20	9.039	5
	Total	51.89	9.130	20
Interpersonal Relations	male	55.40	7.845	15
	female	45.80	20.389	5
	Total	53.00	12.290	20
Self-Esteem	male	52.01	9.371	15
	female	50.40	3.209	5
	Total	51.61	8.209	20
Self-Reliance	male	55.63	9.233	15
	female	46.00	4.637	5
	Total	53.22	9.254	20

*lower scores indicate more problems

Table 21: Multivariate Analysis of Variance for Gender (Adaptive Skills)

Wilk's L	*F*	Hypothesis *df*	Error *df*	*p*	eta^2
.588	2.632	4	15	.076	.412

Two additional (separate) one-way MANOVA's were completed with "treatment intensity" and "age when treatment started" as IV's. Separate one-way MANOVA analysis for each IV did not indicate any significant differences for either IV factor when DV's were combined (Table 22). The absence of a statistically significant main effects for each analysis did not provide the needed support for the hypothesis, thus no further analysis were conducted.

Table 22: One-way MANOVA Results for Treatment Intensity and Age at TX Start

	Wilk's L	*F*	Hypothesis *df*	Error *df*	*p*	eta^2
Intensity of Treatment	.579	2.547	4	14	.086	.421
Age at Tx Start	.580	1.094	8	28	.396	.238

Finally, separate one-way MANOVA's were conducted for each IV factor separately (gender, treatment intensity, age at treatment start) based on *caregiver*s report. The DV's utilized in this analysis were adaptive scales from the BASC-2 parent rating form. They included adaptability, social skills, and leadership. Results of the three separate one-way MANOVA's did not indicate any significant differences. That is, combined DV's did not differ significantly based on gender, treatment intensity, or age at treatment start. The absence of a statistically significant main effects for each analysis did not provide the needed support for the hypothesis, thus no further analysis were conducted.

CHAPTER V: DISCUSSION

This chapter will first summarize the results of this investigation in the context of existing research and theory. Next, the applications of these results to clinical practice will be discussed. Finally, limitations of this study will be explored and directions for future research will be discussed.

SUMMARY AND INTEGRATION OF FINDINGS

The most common form of childhood cancer is Acute Lymphoblastic Leukemia (ALL), which affects approximately 1 - 3.4 children per 1,000 (Waber & Mullenix, 2000; Ries, Miller & Hankey, 1994). In the past twenty years, advances in medicine and technology have drastically increased the survivor rates of children. Today, most individuals with ALL can expect to exceed the 80-85% expected survival rate (Waber & Mullenix, 2000; Daly et al., 2008; Mulhern & Butler, 2005). Although the increased rate of survival is promising, it poses some serious questions about the effects of having cancer, the treatment that children receive, and the long-term effects they experience after remission has been achieved.

Most research investigating issues related to late effects often focus on neurocognitive effects that occur as a result of treatment. Less studied, however, are the long-term psychological effects experienced by cancer survivors months, to years, later. Additionally, the limited research for long-term psychological effects is limited, and often inconsistent. For example, some literature suggests that damage to white matter due to the toxicity of treatment can lead to deficits in emotional functioning (e.g. changes in personality, apathy, increased levels of anxiety and depression, etc.) (Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000) whit other studies have specifically suggested that survivors experience increased rates of depression, anxiety, and low self-

esteem (Koocher, O'Malley, Gogan, & Foster, 1980; Kazak, 1994). In contrast others have found that survivors experience healthy long-term psychological adjustment (Brown et al., 1992; Fritz, Williams & Amylon, 1988; Greenberg, Kazak, & Meadows, 1989; Novakovic, et al. 1996, Verrill et al. 2000; Noll, et al., 1999). Additionally, recent innovations in the way that cancer is treated in children have largely eliminated the use of radiation. Consequently, only the most recent studies have investigated the effects that chemotherapy alone (which often contains methotrexate, a highly neurotoxic treatment) has on the developing child and his or her brain (Anderson & Kunin Batson, 2009).

The primary focus of this study was to investigate, and aim to clarify, the specific types of emotional and behavioral late effects that child and adolescent ALL cancer survivors experience months to years after remission. Although emotional and behavioral late effects are hypothesized to occur by some, and not by others, many investigations have suffered from methodological challenges. These include rapidly changing treatment protocols, small sample sizes, and heterogeneous populations (Anderson & Kunin Batson, 2009). Some investigations have also investigated psychological effects while children and adolescents were undergoing treatment (Liang, et al., 2006) and not after they were still in remission.

Summary of Findings for Gender

Research question 1 explored whether there were gender differences in *self-reporting* of depression, anxiety, attention, and hyperactivity symptoms. The result of the MANOVA analysis was not significant and did not support the overall hypothesis that emotional and behavioral functioning significantly differed when the DV's were combined. Thus, no further statistical analysis was conducted.

Despite the lack of significance, narrative and informal analysis was utilized to describe patterns in the data. Although this is not a typical process in statistical analysis,

the fact that this was a pilot study made it important to describe the data anecdotally to help guide future research. In doing so, patters in the data indicated that females reported more hyperactive symptoms than their male counterparts. Anecdotal analysis coincides with research that has shown developmental differences in the mass of white matter found in developing brains, with females having less white matter than males. Specifically, the informal analysis regarding gender's effect coincided with research that indicated exposing the brain to neurotoxic chemicals via chemotherapy treatment can leave the female brain more susceptible to "neurotoxic insult" (Buizer, de Sonneville, PhD, van den Heuvel – Eibrink, & Veerman, 2005) in the form of white matter damage. White matter damage is thought to lead to deficits in executive function. Because executive function is important for inhibitory control (Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000), deficits in this area can lead to increased hyperactivity.

Research question 4 similarly explored whether there were gender differences in depression, anxiety, attention and hyperactivity symptoms but was based on *caregiver* reports. The result of the MANOVA analysis was not significant and did not support the overall hypothesis that emotional and behavioral functioning significantly differed when the DV's were combined.

Overall Findings for Gender

Statistical analysis of emotional and behavioral functioning did not indicate significant differences based on gender; however, anecdotal analysis indicated that female survivor's reported more problems with hyperactivity on average than males. In contrast, caregivers reported that males (t-score=54.11) experienced more hyperactive difficulties than females (t-score=50.60). Further analysis of the raw data (Table 23) suggests that survivors and caregivers disagree on the severity of symptoms for anxiety and depression. That is, females reported more difficulty with anxiety (t-score=55.00)

and caregivers reported that males had more difficulty in this area (t-score=50.90). Additionally, although males reported more symptoms related to depression (t-score=50.51), caregivers reported more depressed symptoms in females (t-score=59.60).

There was some agreement in symptom reporting, however. Caregiver and survivors reported more attention problems in females overall (t-score=52.60, t-score=57.20, respectively) than in males. Although the differences in attention based on gender were not significant, the fact that females had a higher (more problematic) mean score for attention further supports the hypothesis that females are more likely to have white matter damage after chemotherapy treatment leading to executive functioning deficits (such as problems with attention and hyperactivity). Additionally, caregivers' mean score for attention was almost in the at-risk range as dictated by the BASC-2.

Table 23: Mean Gender Differences Between Reporters

	Gender	Self-Report Means	Caregiver-Report Means
Anxiety	male	50.11	50.90
	female	55.00	48.60
	Total	51.33	50.32
Depression	male	50.51	44.51
	female	45.80	59.60
	Total	49.33	46.53
Attention	male	49.75	51.04
	female	57.20	52.60
	Total	51.61	53.18
Hyperactivity	male	48.75	54.11
	female	58.20	50.60
	Total	51.11	53.24

Summary of Findings on Treatment Intensity

Research question 2 investigated whether there were differences in depression, anxiety, attention and hyperactivity symptoms based on treatment intensity as reported by *survivors*. Treatment intensity was divided into high intensity chemotherapy and low intensity chemotherapy. The result of the MANOVA analysis was not significant and did not support the overall hypothesis that emotional and behavioral functioning significantly differed when the DV's were combined. The results of this analysis were not consistent with research that high-intensity CNS-directed chemotherapy can lead to difficulties with attention and hyperactivity due to inadvertent damage to white matter (Buizer, et al., 2006).

Research question 5 investigated whether there were differences in depression, anxiety, attention and hyperactivity symptoms based on treatment intensity as reported by *caregivers*. Treatment intensity was divided into high intensity chemotherapy and low intensity chemotherapy. Identical to survivors' analysis, result of the overall MANOVA, did not suggest any significant differences in symptoms based on treatment intensity. As was stated above, the results of this analysis were not consistent with research that difficulties with attention and hyperactivity are positively correlated with higher intensity chemotherapy-only treatment (Buizer, et al., 2006).

Overall Findings for Treatment Intensity

Results from analysis of treatment intensity did not suggest any significant differences in reporting of attention or hyperactive symptoms, as the research would suggest. Additionally, no differences in anxiety or depression were found. In particular, some purport that attentional difficulties and problems with inhibitory control are the direct result of white matter to the brain resulting from high-intensity chemotherapy (Buizer, et al, 2005).

Although the analysis conducted did not reveal any statistically significant findings, analyzing patterns of the BASC-2 data provides more anecdotal information (Table 24), which may be useful for directing future research. Generally, survivors and caregivers reported more difficulty with anxiety, depression and attention for those who underwent lower-intensity treatment. This is in stark contrast to research by Buizer (2006) and colleagues who found that high-intensity chemotherapy was directly related to attention difficulties. Similarly, caregivers also reported on average more hyperactive symptoms in those that underwent low-intensity chemotherapy. Survivors that underwent high intensity chemotherapy, however, reported more (t-score=51.50) hyperactive symptoms than those who underwent lower-intensity chemotherapy (t-score=50.48). Despite differences in reporting and the lack of support by existing research, no reported means (whether for those who underwent high or low intensity treatment) were in the at-risk or clinically significant range of severity as described by the BASC-2.

Table 24: Means on self-report BASC-2 for Intensity

	Intensity	Self-Report Means	Caregiver Means
Anxiety	low	53.28	52.57
	high	48.33	44.17
	Total	51.72	49.92
Depression	low	52.90	47.28
	high	43.00	44.83
	Total	49.77	46.50
Attention	low	53.63	53.73
	high	46.83	52.17
	Total	51.49	53.24
Hyperactivity	low	50.48	56.52
	high	51.50	47.50
	Total	50.80	53.67

Summary of Findings on Age at Treatment Initiation

Research question 3 investigated whether there were *survivor*-reported differences in depression, anxiety, attention and hyperactivity symptoms based on when they began treatment. The age when individuals started treatment was divided into three groups: young (0-4), middle (5-8) and old (≥ 9). The result of the MANOVA analysis was significant and supported the overall hypothesis that depression, anxiety, attention and hyperactivity significantly differ based on age at treatment initiation when DV's were combined. Further exploration using one-way ANOVA's were used as follow up tests for each dependent variable. This analysis did not reveal any significant differences in reporting of emotional or behavioral functioning based on when treatment was started. The fairly uneven number of participants in each age level could have impacted the possibility of finding significant results.

Research question 6 investigated whether there were differences in depression, anxiety, attention and hyperactivity symptoms based on treatment intensity as reported by *caregivers*. Results of the overall MANOVA did not suggest any significant differences in symptoms based on age when treatment started. As was stated above, the results of this analysis could have been due to the uneven number of participants.

Overall Findings for Age at Treatment Initiation

Results from analysis of age at treatment start suggested significant differences in reporting of anxiety, depression, hyperactivity and attention, (as reported by survivors); however, follow-up ANOVA results were not significant. As was stated earlier, the unequal participant numbers could have impacted this analysis across groups. Despite this limitation, anecdotally analyzing the BASC-2 data further reveals that survivors who started treatment between 0-4 years old reported more symptoms of depression,

hyperactivity and attention than those who started treatment at an older age (Table 25). Additionally, survivors who started treatment between 0-8 years of age reported more symptoms of anxiety. Caregiver's means also indicated that younger children experienced more symptoms of anxiety and hyperactivity than middle and older children. Finally, caregiver means also suggest that children who started treatment between ages 0-8 also had more symptoms of depression and attention difficulties.

Overall, anecdotal analysis of means coincides with previous research that indicates children who start treatment at an earlier age experience more emotional and behavioral problems. Specifically, anxiety and depression are thought to impact those who were younger at the time that treatment began because younger children use less developmentally mature strategies to cope with high levels of stress. Unlike young children, adolescents are believed to handle stressors, like cancer, more effectively and efficiently by employing a conglomerate of coping strategies involving both abstract and pragmatic methods; thus it is believed by some that younger children will ultimately have a more difficult time regulating their emotions and behavior (Band & Weisz, 1988; Worchel, Copeland & Barker, 1987). Additionally, exposure of less developed brains to neurotoxic chemicals in less developed brains can lead to white matter damage, leading to executive functioning deficits and inadvertently causing deficits with attention and hyperactivity (Filley & Leinschmidt, 2001; Hill, Cooper & Perry, 2000).

Table 25: Means on self-report BASC-2 for age at TX initiation

	Age	Self-Report Means	Caregiver-Report Means
Anxiety	young (0-4)	50.76	53.55
	middle (5-8)	56.56	48.41
	oldest (≥ 9)	43.00	42.33
	Total	51.33	50.32
Depression	young	51.85	46.27
	middle	44.56	48.43
	oldest	49.67	43.67
	Total	49.33	46.53
Attention	young	54.24	53.36
	middle	50.27	53.75
	oldest	44.67	51.33
	Total	51.61	53.18
Hyperactivity	young	53.92	55.36
	middle	48.52	51.28
	oldest	46.00	49.33
	Total	51.11	53.24

Summary of Findings for Differences in Survivor and Caregiver-Reported Symptoms

Research question 7 investigated whether there were significant differences in survivor and caregiver reports of depression, anxiety, attention and hyperactivity. The result of the MANOVA analysis was not significant and did not support the overall hypothesis that caregivers would report significantly more symptoms of attention and hyperactivity than survivors.

Overall Findings for Differences in Survivor and Caregiver-Reported Symptoms

Results from the analysis of potential differences in reporting between survivors and caregivers were not significant. This was in contrast to expected results that caregivers would report more externalizing symptoms because problems with attention

and hyperactivity are much more observable, than problems with anxiety or depression. Studying the patterns in BASC-2 data (Table 26) reveals that overall mean scores are inconsistent with this investigation's hypothesis. For example, caregivers' mean score for depressed symptoms and problems with attention was higher than survivors' mean score. Alternatively, survivors' mean score for anxiety and hyperactivity was higher than mean score for caregivers'. The inconsistent findings suggest that further research into the different perspectives of survivors and caregivers should be addressed in the future.

Table 26: Means and std. deviations for differences in reporting between survivor and caregiver

	Reporter	Mean	Std. Deviation	N
Depression	child	49.33	13.906	20
	parent	53.18	12.045	20
	Total	51.25	12.987	40
Anxiety	child	51.33	12.087	20
	parent	46.53	8.548	20
	Total	48.93	10.616	40
Attention	child	51.61	10.352	20
	parent	53.24	11.176	20
	Total	52.42	10.665	40
Hyperactivity	child	51.11	7.677	20
	parent	50.32	10.068	20
	Total	50.72	8.846	40

OVERALL FINDINGS

The age when treatment started was a focus of this investigation because research has suggested younger children are more susceptible to treatment-related neurotoxicity such as toxic leukoencephalopathy (Davis, Hoffman, Pearl & Braun, 1986). Additionally, because younger children have not typically navigated and developed emotion-based coping strategies at the level that older children and adolescents have, we would expect younger children to have a more difficult time finding ways to cope with their stressful

experience (Lazarus, 1984). Thus, this investigation expected to find that younger individuals and caregivers reported more difficulty with anxiety, depression, attention and hyperactivity. Results overall suggested that survivor reports of difficulties differed significantly based on when treatment started; however, follow-up one-way ANOVA's were not significant. Anecdotal analysis was thus conducted in hopes of gleaning additional information to guide future research. Informal analysis of the data suggested that survivors who started treatment between 0-4 years old reported more symptoms of depression, hyperactivity and attention than those who started treatment at an older age. Additionally, survivors who started treatment between 0-8 years of age reported more symptoms of anxiety. Caregiver's means also indicated that younger children experienced more symptoms of anxiety and hyperactivity than middle (4-8) and older (≥ 9) children. Finally, caregiver means also suggested that children who started treatment between ages 0-8 also had more symptoms of depression and attention difficulties. Overall, narrative description of means coincides with previous research that indicates children who start treatment at an earlier age experience more emotional and behavioral problems.

Another focus of this study was to investigate gender's role on emotional and behavioral late effects. Results of MANOVA analyses for both survivors and caregivers were not significant. However, narrative and informal analysis of BASC-2 means suggested that hyperactivity, as reported by survivors, differed based on gender. Specifically, females reported more symptoms of hyperactivity than males. Despite these results, the mean t-score for female hyperactivity symptoms was not severe enough to fall into the at-risk or clinically significant category as described by the BASC-2. So although female survivors of leukemia reported more difficulty in this area, it does not appear that hyperactivity is a clinically significant late-effect resulting from leukemia and

its treatment. Interestingly, caregivers on average reported that males exhibited more difficulty with hyperactivity. Although reports by caregivers did not significantly differ based on gender, the difference in reporting may be due to perceptions that males exhibit hyperactivity in much more obvious, observable ways. While females may be subtler and less obvious in the way they exhibit hyperactivity.

This study also investigated whether treatment intensity would lead to significant differences in reporting of attention, hyperactivity, depression and anxiety. Whereas research suggested a link between high-intensity chemotherapy and attentional/hyperactive deficits (Buizer, et al, 2005), this analysis did not reveal any significant differences for either survivors or caregivers. Narrative analysis of BASC-2 means indicated that survivors and caregivers, on average, reported more difficulty with anxiety, depression, and attention in those that underwent low-intensity chemotherapy (although these results were not significant). These results were unexpected and not supported by current research in this area.

Finally, exploratory analysis was conducted to determine whether survivors or caregivers significantly differed in adaptive functioning. Results did not indicate any significant differences. However, anecdotal analysis of the BASC-2 data was conducted in order to guide future research and indicated that males differed in their report of self-reliance. Specifically, males reported more self-reliance than females. Even though males reported better self-reliance, females' mean scores were still within normal limits.

Overall, findings of this study suggested significant differences in reporting of anxiety, depression, attention and hyperactivity based on the age when treatment was initiated; however, further analysis was not significant. All other hypotheses of this study were not significant. Thus, a major portion of this pilot study relied on narrative and informal description of the data in the hopes of guiding future research. Although this

approach discerned interesting information about late-effects in children that survived ALL, none of the differences discussed differed significantly based on gender, or the intensity of treatment. Most importantly, narrative and informal analysis of BASC-2 scales and means did not indicate at-risk or clinically significant problems. That is, ALL survivors in this study reported emotional, behavioral and adaptive functioning that was within normal limits.

IMPLICATIONS FOR CLINICAL PRACTICE

The goal of this study was to determine whether survivors of leukemia experienced significant late-effects months, to years, after they have remitted. Investigating potential late-effects is fundamental to identifying potential risk factors that may make it more likely for individuals to experience negative effects post-remission. Identifying risk factors can further aid oncologists, psychologists, and other medical team members in choosing the best possible treatment strategies for newly diagnosed children and adolescents in order to prevent late effects (as much as possible) before they happen. (Anderson & Kunin Batson, 2009). Although preventative measures are undoubtedly important, at present we must also confront the issues that the ever-increasing number of survivors (who have already undergone highly traumatic and toxic treatments) are, or likely will be, experiencing in the future.

While the main goal for these children was once survival, it has now shifted to understanding ways to screen for and identify late effects since up to 80-85% of children exceed the 5-year expected survival rate. Results from this study can guide early intervention and promote more individualized screening of individuals for late effects.

For example, narrative and informal analysis suggested that females report more hyperactive symptoms than their male counterparts. In contrast, caregivers reported more hyperactive problems for males. The difference in reporting was hypothesized to occur

because females' hyperactive behaviors may occur in more subtle ways. Thus, care during screening visits should focus on individualizing questions about hyperactivity towards the way females may exhibit hyperactivity (i.e. fidgeting at their desk, shaking their leg, 'nervous' tics, etc. vs. getting out of their desk, running around the home or classroom, playing rough, getting in trouble for impulsive behaviors, etc.).

Additionally, narrative and informal analysis of the data supported present research that indicates children are at risk for more late-effects when they start treatment earlier. If this is due to chemotherapy, physicians and researchers are already implementing and promoting less toxic ways to treat leukemia. However, if individuals experience more psychological and behavioral late effects due to deficits in coping, then it will be important for psychologists to help find ways to teach young children how to cope with significant amounts of stress in age appropriate ways.

LIMITATIONS

There are limitations to the current study. One of the largest limitations of this study is that it was not a repeated measures design and did not produce data that could be examined over time with the same subjects. Had this investigation followed these individuals over time, analysis could have resulted in significantly more information than was gathered presently. Additionally, the lack of pre- and post- assessment makes it difficult to conclude whether these individuals were already struggling with emotional or behavioral problems prior to their diagnosis, although particularly for the younger patients it is unlikely that emotional/behavioral difficulties had emerged.

Another limitation of this investigation was the small sample size, which weakened the power to detect differences between groups. Additionally, if more participants had been recruited or more data had been available, more detailed analysis could have been conducted such as investigating the interactions between genders, ages

at treatment start, and treatment intensities. Also, the small sample size restricted the number of dependent variables that could be addressed at any given time. Thus, the investigator had to narrow down the dependent variables to only those that were clearly supported in previous research. Not including other subscales from the BASC-2 also eliminated the possibility of performing more in depth exploratory analysis. Additionally, because of the small sample sizes, participants across groups were sometimes unequal as much as 3:1. Gender, for example, was relatively unequal (although) consistent with the gender distribution for leukemia (Leukemia and Lymphoma Society, 2010). Treatment intensity was also unequal as there were almost double the participants that underwent low-intensity chemotherapy as compared with high-intensity chemotherapy. This distribution in the real-world, however, is similar as high-intensity chemotherapy treatment for leukemia patients is not as commonly used as it is for other types of cancers. Additionally, although age at treatment start significantly affected the combined DV's, the follow up ANOVA's were not significant and may have been impacted by the very small sample size in the 'old' age group (N=3).

Another limitation of this study was the variability of treatment that the participants received. That is, it can generally be assumed that low-risk patients received lower doses of chemotherapy, and high-risk patients receive higher doses. However, the actual drugs used can vary and depend on the individual's initial response (or lack thereof) to treatment, the randomization of the patient to specific treatment groups, and the constantly changing treatment protocols and regimens, etc. Thus, these slight differences in treatment protocol may have had a significant impact on this study.

Finally, the BASC-2 and other self-report measures are inherently limited because they can be significantly affected by response bias. If an individual is defensive or lacks

insight into their problems, they may not report any significant symptoms. Add to that the small sample size, and it can make it very difficult to find any significance.

DIRECTIONS FOR FUTURE RESEARCH

There are many reasons why investigations about the psychological and behavioral impact of Acute Lymphoblastic Leukemia should continue. First, it is the most common form of childhood cancer and affects anywhere between 1 – 3.4 children per 10,000 (Waber & Mullenix, 2000; Ries, Miller & Hankey, 1994). Additionally, the diagnosis of childhood cancer today is met with some semblance of hope as >80% of those affected survive the ordeal. With increased rates of survival, however, comes the responsibility of determining how these individuals are ultimately impacted by their diagnosis and treatment.

Neurocognitive disabilities resulting from toxic treatments have been well studied and have resulted in large clinical cooperative groups adopting changes in policy and procedures. For example, in 1993, various groups came together to adopt risk-classification procedures in order to reduce unnecessary exposure to high levels of chemotherapy. Unfortunately, many of these large cooperative-groups have largely ignored psychological outcomes; individual investigators have conducted the majority of studies investigating the psychosocial and behavioral outcomes of leukemia. The inherent problem being that an individual investigator at a smaller institution will not have the same resources of the larger, more organized groups to promote policy and changes in practice (Armstrong & Reaman, 2005).

It is pertinent that future investigations regarding psychological outcomes be conducted in conjunction with cooperative groups that can offer a number of benefits and reduce limitations in studies. For example, cooperative groups can be composed of many numbers of large institutions. This can allow investigators to access large numbers of

participants with similar disease profiles, and that are undergoing identical treatments. As Armstrong and Reaman (2005) indicate, investigations at smaller institutions looking into psychological and behavioral-type effects often include in their studies individuals with a variety of cancers, undergoing different types of treatment (chemotherapy, chemotherapy+radiation, surgery, etc.) making for less than optimal study conditions. This is a large limitation often found in many psychological studies of cancer's late effects (Armstrong & Reaman, 2005). Additionally, cross-disciplinary investigations within large cooperative groups can allow for more access to non-psychological data that can improve our understanding of psychological and behavioral late-effects in children. Information such as genetic, biological and imaging data may shed light on to previous unknown associations and associated risk factors.

In the past 20 years, we have learned about the harmful physical, physiological, and cognitive effects that high intensity chemotherapy, coupled with cranial radiation can have on the developing child brain. Along with this knowledge came change such as classifying risk, and reducing the use of radiation in children altogether. It also led to increased awareness by physicians and parents about taking preventative measures and identifying risk factors that would make it less likely for a child to experience negative, physiological late effects (Armstrong & Mulhern, 1999). Despite, our advancement in understanding the overall effects of this disease, future research must continue to focus on increasing our knowledge concerning psychological outcomes. In particular, future research should continue to focus on increasing our understanding about late effects that result from cancer treatment, risk factors, and interventions that prevent or alleviate late effects (Armstrong & Reaman, 2005).

Overall, the need for more organized, cooperative investigations that can combine cross-disciplinary information will be the next step in understanding the mechanisms of

psychological and behavioral late effects. The resulting model of interactions will undoubtedly be complex as each case contains idiosyncrasies. One individual with the same disease, who is treated in the exact same way as another, may have very different outcomes. The combination of other information such as genetic-risk and protective factors, concurrent genetic learning-problem risks, environmental factors, level of family dysfunction, adaptations to stress and coping, etc., may contribute to psychological and behavioral outcomes. Only when large institutions begin to work more closely together in this endeavor will information into late effects lead to more targeted prevention and treatment.

Appendix

Parent/Guardian Informed Consent Agreement

Please read this consent agreement carefully before you decide to participate in the study. Your child will also receive an assent form; please review the assent form with your child.

Hello:

My name is Michael Garcia and I am a doctoral student in School Psychology (Educational Psychology Department) at the University of Texas at Austin. I am conducting an investigation at the LIVESTRONG Survivorship Center at Dell Children's Hospital. This investigation is part of my dissertation looking into potential emotional and behavioral problems that survivors of Acute Lymphoblastic Leukemia may experience months, to years after completing treatment. Your child and your child's teacher (should you choose to give consent) will also be asked to fill out similar questionnaires.

Please read the following carefully and thank you in advance for your consideration in participating in my study.

Sincerely,

Michael I. Garcia, M.A.
Doctoral Candidate
The University of Texas at Austin
School Psychology
Educational Psychology

Purpose of the research study: The purpose of this study will be to investigate delayed emotional and behavioral problems that may result from Acute Lymphoblastic Leukemia diagnosis and treatment in child and adolescent survivors. This investigation also aims to investigate risk factors that may make it more likely to develop emotional and behavioral problems in the future. Examples of potential risk factors include: intensity of treatment, addition of radiation to treatment, age at diagnosis, and gender.

The most common form of childhood cancer is Acute Lymphoblastic Leukemia (ALL). The increased chance of survival poses challenges for patients and their families; for example, patients treated for ALL may experience short- and long-term physiological effects due to treatment. However, less understood is whether treatment and the experience of battling a life-threatening illness lead to long-term *emotional* and *behavioral* problems for pediatric oncology survivors.

In researching potential emotional and behavioral difficulties, and the impact of certain risk factors, this investigation hopes to provide useful information that can help with the development of programs that may help to prevent and improve long-term emotional and behavioral outcomes for pediatric survivors of ALL.

What will you and your child do in the study: If you and your child consent to participate in this investigation, you will receive two different surveys through U.S. Mail (one for the primary caregiver and one for your child). You and your child will be asked to fill out the survey which will ask about your child's current emotional and behavioral functioning. If you also consent to and sign the "Exchange of Information" form, one of your child's teachers will be sent a similar survey that will ask him or her to answer questions regarding your child's current emotional and behavioral functioning. The answers to all surveys, as well as any demographic information that is collected, will be used to determine any problematic emotional and behavioral difficulties that pediatric cancer survivors may or may not experience after having completed treatment.

The primary investigator may also contact you to answer any questions or address any concerns you have. You are also encouraged to contact the investigator if you have any questions and/or concerns about you or your child's participation.

While it is important to receive all materials fully completed, you and your child may skip any question that may make you or your child feel uncomfortable. You and your child may stop the survey at any time.

Time required: The survey will require about 20 minutes of of your time. **Your child should expect to spend approximately 30 minutes to complete their survey.**

Risks: There are no anticipated risks in this study.

Benefits: There are no direct benefits to you or your child for participating in this research study. The study may help us understand delayed, emotional and behavioral problems that ALL survivors may experience. In addition, results of this investigation may make it easier to develop ways to prevent and address emotional and behavior problems that ALL survivors may experience.

Confidentiality: The information that your child gives or that you give in the study will be handled confidentially. Your information will be assigned a code number. The list connecting your child's name and/ or your name to this code will be kept in a locked file. When the study is completed and the data have been analyzed, this list will be destroyed. Your child's name and/or your name will not be used in any report.

The information that your child gives or that you give in the study will be anonymous. Your child's name and/or your name will not be collected or linked to the data.

Voluntary participation: Your child's participation and/or your participation in the study is completely voluntary.

Right to withdraw from the study: You have the right to withdraw your child and yourself from the study at any time without penalty.

How to withdraw from the study: If you and/or your child want to withdraw from the study, tell the researcher. There is no penalty for withdrawing. If you would like to withdraw after your materials have been submitted, please contact the principal investigator, Michael I. Garcia at (512) 671-0973 or at Michael.garcia@mail.utexas.edu.

Payment: You will receive no payment for participating in the study.

If you have questions about the study, contact:
Michael I. Garcia
School Psychology Program
Educational Psychology Department
1 University Station D5800
Austin, TX 78712
Telephone: (512) 671-0973

Faculty Advisor's Name
Rachel Robillard, Ph.D., LSSP

4810 B Spicewood Springs Rd.
Austin, TX 78759
robillard@alumni.utexas.net
Telephone: (512) 934-7858

If you have questions about your rights in the study, contact:
Sharon Horner, RN, PhD
Brackenridge Hospital's IRB Chairman
601 E 15th Street
Austin, Texas 78701
(512) 324-7991.

Agreement:
I agree to allow my child to participate in the research study described above.
I agree to participate in the research study described above. I understand that I can withdrawal my consent at any time.

Signature: _____

Printed Name: _____

Date: _____

You will receive a copy of this form for your records.

TEMA CONSENTIMIENTO/PERMISO DE LOS PADRES
Por favor, lea este acuerdo de consentimiento cuidadosamente antes de decidir participar en el estudio. Su hijo también recibirá un formulario de consentimiento, por favor revise el dictamen forma con su hijo.

Hola:

Mi nombre es Michael García y yo soy un estudiante de doctorado en la Escuela de Psicología (Departamento de Psicología de la Educación) en la Universidad de Texas en Austin. Estoy realizando una investigación en el Centro de LIVESTRONG supervivencia de Dell Children's Hospital. Esta investigación es parte de mi disertación y estoy estudiando problemas emocional y problemas de comportamiento que los supervivientes de leucemia linfoblástica aguda pueden experimentar meses o años después de terminar el tratamiento. Mi estudio incluye algunos cuestionarios sobre las emocionales y comportamiento de su niño. Su hijo y el maestro de su niño (si usted elige dar su consentimiento) también se pedirá que rellene cuestionarios similares.

Por favor, lea cuidadosamente el siguiente y gracias de antemano por su consideración en participar en mi estudio.

Atentamente,

Michael I. Garcia, M.A.
Doctoral Candidate
The University of Texas at Austin
School Psychology
Educational Psychology

Propósito del estudio de investigación: El propósito de este estudio será para investigar el comportamiento emocional y los problemas que pueden derivarse de leucemia linfoblástica aguda (ALL) diagnóstico y tratamiento en niños, niñas y adolescentes sobrevivientes. También, queremos investigar los factores de riesgo que pueden hacer más propensos a desarrollar emocional y problemas de comportamiento en el futuro. Ejemplos de los posibles factores de riesgo incluyen: la intensidad del tratamiento, además de la radiación para el tratamiento, la edad, y sexo.

La forma más común de cáncer infantil es leucemia linfoblástica aguda (ALL). El aumento de posibilidades de supervivencia plantea retos para los pacientes y sus familias. Por ejemplo, los pacientes tratados de ALL pueden experimentar a corto y largo plazo efectos fisiológicos debido al tratamiento. También queremos comprender si el tratamiento puede conducir a problemas emocionales y dificultades de comportamiento en el futuro de los supervivientes de oncología pediátrica.

Esta investigación aspira a proporcionar información útil que le puede ayudar en el desarrollo de programas que pueden ayudar a prevenir y mejorar a largo plazo del comportamiento emocional y pediátricos de los resultados de supervivencia de TODOS .

¿Qué va a usted y su niño hacer en el estudio: Si usted y su niño dan consentimiento a participar en esta investigación, usted recibirá dos cuestionarios diferentes, (una para el cuidador principal y uno para su hijo). Usted y su niño se le pedirá que rellene el cuestionario que le preguntará acerca de su actual del niño emocionales y de conducta en funcionamiento. Si, además, usted da consentimiento y firma el "Intercambio de Información" forma, uno de los maestros de su hijo se enviará un cuestionario similar que pregunta sobre los emocionales y de conducta en funcionamiento. Las respuestas de cada cuestionario, así como cualquier información demográfica que se recoge, se utilizarán para determinar las problemáticas emocionales y conducta dificultades que sobrevivientes de cáncer pediátrico pueden tener después de completar el tratamiento.

El principal investigador también podrá contactar usted para responder a cualquier pregunta o resolver cualquier inquietud que usted tenga. También se le anima a ponerse en contacto con el investigador, si usted tiene cualquier pregunta o preocupaciones acerca de la participación de usted y su hijo.

Es importante para recibir todos los materiales totalmente completado. Pero usted y su niño pueden saltar cualquier pregunta si se sienten incómodo. Usted y su niño pueden dejar el estudio en cualquier momento.

Tiempo requerido: El estudio se requieren alrededor de 20 minutos de su tiempo. Su hijo debe esperar a pasar unos 30 minutos para completar su cuestionario.

Riesgos: No hay riesgos previstos en el presente estudio.

Ventajas: No hay beneficios directos para usted o su hijo si participan en este estudio de investigación. El estudio puede ayudarnos a comprender problemas emocionales y problemas de comportamiento que algunos supervivientes pueden experimentar. Además, los resultados de esta investigación puede ayudar a desarrollar medios para prevenir y resolver problemas emocionales y problemas de conducta que supervivientes de ALL a la mejor pueden experimentar.

Confidencialidad: La información que da usted o su hijo se tratarán confidencialmente. Su información se le asignará un número de código. La lista de conectar el nombre de su hijo y su nombre a este código se mantendrá en un archivo bloqueado. Cuando el estudio se ha completado y los datos han sido analizados, esta lista será destruido. El nombre de su hijo y su nombre no va a ser utilizada en cualquier informe.

La información que usted o su hijo da en el estudio será anónimo. El nombre de su hijo y su nombre no serán recogidos o vinculada a los datos.

Participación voluntaria: La participación de su hijo y su participación en el estudio es totalmente voluntaria.

Derecho a retirarse del estudio: Usted tiene el derecho a retirar la participaron de usted y su hijo en este estudio en cualquier momento sin penalización.

¿Cómo retirar del estudio?: Si usted o su hijo quiere retirarse del estudio, decir el investigador. No hay pena para la retirada. Si a usted le gustaría retirarse después de sus materiales se han presentado, por favor, póngase en contacto con el investigador principal, Michael I. García en el (512) 671-0973 o en Michael.garcia@mail.utexas.edu.

Pago: Usted recibirá ningún pago por su participación en el estudio.

Si usted tiene preguntas acerca del estudio, póngase en contacto con:
Michael I. Garcia
School Psychology Program
Educational Psychology Department
1 University Station D5800
Austin, TX 78712

Telephone: (512) 671-0973

Asesor de la Facultad nombre
Rachel Robillard, Ph.D., LSSP
4810 B Spicewood Springs Rd.
Austin, TX 78759
robillard@alumni.utexas.net
Telephone: (512) 934-7858

Si usted tiene preguntas acerca de sus derechos en el estudio, póngase en contacto con:

Sharon Horner, RN, PhD
Brackenridge del hospital Presidente IRB
601 E 15th Street
Austin, Texas 78701
(512) 324-7991.

Acuerdo: Estoy de acuerdo en permitir a mi hijo a participar en el estudio de investigación que se ha descrito anteriormente. Estoy de acuerdo en participar en el estudio de investigación que se ha descrito anteriormente. Yo entiendo que puede retirar mi consentimiento en cualquier momento.

Firma: _____

Nombre: _____

Fecha: _____

Usted recibirá una copia de este formulario para sus registros.

Minor Informed Assent Agreement 13-17
Please read this assent agreement with your parent(s) or guardian(s) before you decide to participate in the study. Your parent or guardian will also give permission to let you participate in the study.

WHAT IS THIS INVESTIGATION ABOUT? Hello, my name is Michael Garcia and I am a graduate student in School Psychology at the University of Texas at Austin. I would like to tell you a little about my study. You may remember that when you were being treated for Leukemia, you sometimes experienced negative side effects of treatment such as hair loss, vomiting, loss of appetite, stomach aches, pains, etc. You may also have experienced problems with thinking, memory, concentration, balance, speech and vision problems. Fortunately, a lot of those effects went away when you completed treatment; for some, however, those side effects remain. Although we know a lot about the potential physical effects of treatment, we still do not know a lot about how your experience and the treatments you received (like chemotherapy and/or radiation) affect emotions and behavior in children and adolescents years later.

Through this investigation, I would like to find out how you are doing (emotionally and behaviorally) since you stopped receiving treatment. If we find, for example, that individuals like you report a lot of emotional problems, then we may be able to help develop programs to help individuals like yourself feel better. In addition, it is my hope that through this investigation, we might be able to identify certain risk factors that may make it more likely for survivors of Leukemia to experience negative emotions and behavior problems later in life.

WHAT DO I HAVE TO DO? As part of our study, we would like to ask you to answer some questions regarding your emotions and behavior. The questionnaire will take approximately 30 minutes of your time to complete. You can do it all at once, or you can do it in chunks. We will also ask one of your parents, and one of your teachers to fill out the same type of form.

If you participate in the study, you may be uncomfortable if you are not used to answering questions about your emotions. However, if you get to a question and you do not want to answer it, you can skip it. If you start the questionnaire and realize you don't want to complete it, you can stop at any time with no penalty to you or your family.

RISKS AND BENEFITS: We do not believe that there are any risks to you in this study. If you participate in this study, there will not be any direct benefit to you. However, your answers to these questions will help us better understand emotional and behavioral functioning in ALL survivors, which may help us prevent those problems from occurring in children and adolescents who may be diagnosed with ALL in the future.

CONDIFENTIALITY: The information that you give to us during this study will be kept private. Your name will not be used, and the list linking the code name assigned to your real name will be destroyed after all the data is collected no one who reads about our study will know it was you. We keep things locked up so that only our researchers see them.

DO I HAVE TO PARTICIPATE? You don't have to participate in this study and you can stop doing the study at any time. If you want to stop doing the study, tell your parents and myself, Michael Garcia. If you choose to stop before I am finished with my study, any answers you already gave will be destroyed. There is no penalty for stopping. If you decide that you don't want your materials in the study but you already turned them in, contact Michael Garcia at Michael.garcia@mail.utexas.edu

If you have questions about the study, contact:
Michael I. Garcia
School Psychology Program
Educational Psychology Department
1 University Station D5800
Austin, TX 78712
Telephone: (512) 671-0973

Faculty Advisor's Name
Rachel Robillard, Ph.D., LSSP
4810 B Spicewood Springs Rd.
Austin, TX 78759
robillard@alumni.utexas.net
Telephone: (512) 934-7858

If you have questions about your rights in the study, contact:
Sharon Horner, RN, PhD
Brackenridge Hospital's IRB Chairman
601 E 15th Street
Austin, Texas 78701
(512) 324-7991.

Agreement:
I agree to participate in the research study described above. I understand that I can withdraw my participation in this study at any time.

Signature: _____

Printed Name: _____

Date: _____

You will receive a copy of this form for your records.

Informado Acuerdo 13-17
Por favor, lea el presente dictamen de acuerdo con su padres antes de decidir participar en el estudio. Su padre, madre o tutor también dará permiso para que puedas participar en el estudio.

¿DE QUE SE TRATA ESTA INVESTIGACION? Hola, mi nombre es Michael García y yo soy un estudiante graduado en la Escuela de Psicología de la Universidad de Texas en Austin. Me gustaría decirles un poco acerca de mi estudio. Tu puede recordar que cuando recibiste tratamiento por la leucemia, a veces tuviste negativos efectos secundarios del tratamiento, como la pérdida del cabello, vómitos, pérdida de apetito, dolores de estómago, dolores, etc. Tambien, algunos han experimentado problemas con el pensamiento, la memoria, la concentración, el equilibrio, y problemas de visión. Afortunadamente, muchos de esos efectos se fueron cuando terminaste el tratamiento. Pero para algunos, sin embargo, los efectos secundarios siguen. Aunque sabemos mucho sobre los posibles efectos físicos del tratamiento, aún no sabemos mucho acerca de cómo su experiencia y los tratamientos que ha recibido (como la quimioterapia y / o radiación) afectará a las emociones y el comportamiento en niños y adolescentes en el futuro.

A través de esta investigación, me gustaría saber cómo sobrevivientes de leucemia están funcionando con emocionales y comportamiento, ya que acabaron recibir tratamiento. Si encontramos, por ejemplo, que personas como tu reportan un montón de problemas emocionales, entonces podemos ser capaces de ayudar y desarrollar programas para ayudar a las personas como tu sentar mejor. Además, es mi esperanza que a través de esta investigación, podríamos ser capaces de identificar ciertos factores de riesgo que pueden hacer más probable para los sobrevivientes de leucemia a experimentar emociones negativas y problemas de comportamiento más tarde en la vida.

¿QUÉ TENGO QUE HACER? Como parte de nuestro estudio, nos gustaría pedirle que respondes a algunas preguntas acerca de sus emociones y comportamiento. El cuestionario le tomará aproximadamente 30 minutos de su tiempo. Tu puedes hacer todo a la vez, o puede hacerlo en trozos. También me gustaría pedir a uno de sus padres, y uno de sus maestros a llenar el mismo tipo de formulario.

Si participas en este estudio, puede ser incómodo responder a preguntas acerca de sus emociones. Sin embargo, si llegas a una pregunta que no desea responder, la puede pasar. Si inicia el cuestionario y se da cuenta de que no desea para completar, puede parar en cualquier momento sin penalización para usted o su familia.

RIESGOS Y BENEFICIOS: No creemos que existan riesgos para ti en este estudio. Si participa en este estudio, no habrá ningún beneficio directo para ti. Sin embargo, sus respuestas a estas preguntas nos ayudarán a comprender mejor el comportamiento y emocionales en todos los supervivientes, que nos puede ayudar a prevenir estos problemas se produzcan en los niños, niñas y adolescentes que pueden ser diagnosticados con ALL en el futuro.

CONFIDENCALIDAD: La información que da a nosotros durante este estudio se mantiene como privado. Su nombre no será utilizado, y la lista que el nombre de código asignado a su nombre real será destruido.

¿TENGO QUE PARTICIPAR? Tu no tienes que participar en este estudio y puedes dejar de hacer el estudio en cualquier momento. Si quieres dejar de hacer el estudio, dile a tus padres y yo, Michael García. Si decide dejar de horas antes de que yo termine con mi estudio, ninguna respuesta que ya dio será destruido. No hay pena para detener. Si usted decide que no desea que su material en el estudio pero ya convertido en, póngase en contacto con Michael García en Michael.garcia @ mail.utexas.edu

Si usted tiene preguntas acerca del estudio, póngase en contacto con:
Michael I. Garcia
School Psychology Program
Educational Psychology Department
1 University Station D5800
Austin, TX 78712
Telephone: (512) 671-0973

Faculty Advisor's Name
Rachel Robillard, Ph.D., LSSP
4810 B Spicewood Springs Rd.
Austin, TX 78759
robillard@alumni.utexas.net
Telephone: (512) 934-7858

Si usted tiene preguntas acerca de sus derechos, póngase en contacto con:
Sharon Horner, RN, PhD
Brackenridge Hospital's IRB Chairman
601 E 15th Street
Austin, Texas 78701
(512) 324-7991

Acuerdo:

Estoy de acuerdo en participar en el estudio de investigación se ha descrito anteriormente. Yo entiendo que puede retiro mi participación en este estudio en cualquier momento.

Firma: _____

Nombre: _____

Fecha: _____

Usted recibirá una copia de este formulario para sus registros.

Minor Informed Assent Agreement 7-12
Please read this paper with your Mom or Dad.

Hello, my name is Michael Garcia and I am a student at the University of Texas and I am working on a study to learn about the behavior and feelings of kids like you who were treated for Leukemia. You probably remember that the medicine you took for Leukemia made you feel yucky. Most of the yucky feelings go away when you stop treatment. But sometimes, some children continue to have the same yucky feelings even though they have stopped treatment. Unfortunately, that can lead some kids to feel sad, anxious, or worried, even if the doctor has told them that they are completely healthy.

We don't really know if or why this might happen, but I'd like to find out. If I find that kids like you are experiencing sad feelings long after you finished treatment, then me and others can use that information to help make kids feel less sad, less anxious and less worried.

As part of our study, we would like to ask you to answer a few true/false questions. You can ask your parents for help. It should take you about 30 minutes to fill out, but you can always take breaks and come back to it later if you get tired.

RISKS/BENEFITS: Being in this study will bring you no harm. On the other hand, it won't help you in any way. It will hopefully help us know more about children and any problems with emotion or behavior they may be experiencing after finishing treatment.

CONFIDENTIALITY: Your answers to our questions during this study will be kept private. Your name will not be used, and no one who reads about our study will know it was you. We keep things locked up so no one else can see your answers to our questions.

Your answers to our questions during this study will not have your name on it, so we won't know what answers you give.

DO I HAVE TO PARTICIPATE IN THIS STUDY? You don't have to participate in this study. You can stop doing the study at any time. If you want to stop doing the study, tell your parents and they will get in touch with me. If you choose to stop before we are finished with this study, any answers you already gave will be destroyed. There is no penalty for stopping. If you decide that you don't want your materials in the study but you already turned them in, tell your parents to contact me.

If you have questions about the study, contact:
Michael I. Garcia
School Psychology Program
Educational Psychology Department
1 University Station D5800
Austin, TX 78712
Telephone: (512) 671-0973

Faculty Advisor's Name
Rachel Robillard, Ph.D., LSSP
4810 B Spicewood Springs Rd.
Austin, TX 78759
robillard@alumni.utexas.net
Telephone: (512) 934-7858

If you have questions about your rights in the study, contact:
Sharon Horner, RN, PhD
Brackenridge Hospital's IRB Chairman
601 E 15th Street
Austin, Texas 78701
(512) 324-7991.

Agreement:
I agree to participate in the research study described above. I understand that I can withdraw my participation in this study at any time.

Signature: _____

Printed Name: _____

Date: _____

You will receive a copy of this form for your records.

Menor informado Acuerdo 7-12
Por favor, lea este documento con su mamá o papá.

Hola, mi nombre es Michael García y yo soy un estudiante de la Universidad de Texas y estoy trabajando en un estudio para conocer el comportamiento y los sentimientos de los niños como tú que fueron tratados por leucemia. Probablemente recuerde que el medicamento que tomaste para Leucemia te hizo sentir mal. La mayoría de los mal sentimientos desaparecen cuando se para el tratamiento. Pero a veces, algunos niños siguen teniendo lo mismo mal sentimientos a pesar de que han dejado el tratamiento. Por desgracia, que puede llevar a algunos niños se sienten tristes, ansiosos, o preocupados, incluso si el médico ha dicho que ellos están completamente sanos.

No sabemos muy bien por qué o si esto podría suceder, pero me gustaría averiguarlo. Si me parece que los niños como tú están experimentando sentimientos tristes que mucho tiempo después de terminado el tratamiento, entonces yo y otros pueden utilizar esa información para ayudar a hacer que los niños se siente menos triste, menos ansiosos y menos preocupados.

Parte de nuestro estudio, nos gustaría pedirle que responda a unas cuantas verdadero / falso preguntas. Usted puede pedir a tus padres para obtener ayuda. Hay que tomar unos 30 minutos para llenar, pero siempre puedes tener pausas y volver a ella más adelante, si te cansas.

RIESGO/BENEFICIO Estar en este estudio le llevará ningún daño. Por otra parte, no le servirá de todos modos. Es de esperar que nos ayudan a saber más acerca de los niños con problemas de comportamiento o emoción que se experimenta después de acabado el tratamiento.

CONFIDENCIALIDAD: Sus respuestas a nuestras preguntas durante este estudio se mantiene como privado. Su nombre no será utilizado, y no uno que dice acerca de nuestro estudio se sabe que fue usted. Estamos mantener las cosas bajo llave para que nadie más puede ver sus respuestas a nuestras preguntas.

Sus respuestas a nuestras preguntas durante este estudio no tendrá su nombre en él, por lo que no saben qué respuestas que dar.

¿TENGO QUE PARTICIPAR EN ESTE ESTUDIO? Usted no tiene que participar en este estudio. Usted puede dejar de hacer el estudio en cualquier momento. Si quieres dejar de hacer el estudio, dile a tus padres y que se pondrá en contacto conmigo. Si usted decide parar antes de que se termine con este estudio, ninguna respuesta que ya dio será destruido. No hay pena para detener. Si

usted decide que no desea que su material en el estudio pero ya convertido en, dile a tus padres ponerse en contacto conmigo.

Si usted tiene preguntas acerca del estudio, póngase en contacto con:
Michael I. Garcia
School Psychology Program
Educational Psychology Department
1 University Station D5800
Austin, TX 78712
Telephone: (512) 671-0973

Faculty Advisor's Name
Rachel Robillard, Ph.D., LSSP
4810 B Spicewood Springs Rd.
Austin, TX 78759
robillard@alumni.utexas.net
Telephone: (512) 934-7858

Si usted tiene preguntas acerca de sus derechos en el estudio, póngase en contacto con:
Sharon Horner, RN, PhD
Brackenridge del hospital Presidente IRB
601 E 15th Street
Austin, Texas 78701
(512) 324-7991.

Acuerdo:
Estoy de acuerdo en participar en el estudio de investigación se ha descrito anteriormente. Yo entiendo que puede retiro mi participación en este estudio en cualquier momento.

Firma: _____

Nombre: _____

Fecha: _____

Usted recibirá una copia de este formulario para sus registros

Demographic Intake Form
For Parent or Primary Caregiver
CONFIDENTIAL

Please DO NOT write your name on this form. If asked for specific dates that you are unsure of, PLEASE ESTIMATE.

1. What is your relationship to the child who is participating in this study?

____Mother	____Father
____Grandmother	____Grandfather
____Stepmother	____Stepfather
____Aunt	____Uncle
____Godmother	____Godfather
____Foster Mother	____ Foster Father

____Other (explain)_____

2. What is your child's date of birth? (mm/dd/yy)_____How old is he/she? _____

3. What is your child's sex? ____Male ____Female

4. What was your child's cancer diagnosis? Please be as specific as possible (e.g. high-risk, pre-b cursor ALL) _____

5. When was he/she diagnosed? (mm/dd/yyyy) _____ How old was he/she? _____

6. When did he/she begin treatment? (mm/dd/yyyy) _____

7. How long did he/she undergo treatment? (mm/dd/yyyyy)_____

8. Has your child had a relapse of Leukemia or any other form of cancer? Circle one: YES NO

9. Did your child receive a bone marrow transplant? YES NO

10. Did your child undergo radiation treatment at any time during his/her illness? YES NO

11. Check the highest level of education YOU have completed:
    1. ___sixth grade or less
    2. ___junior high school (9^{th} grade)
    3. ___partial high school (10^{th} grade or 11^{th} grade)
    4. ___high school graduate or G.E.D
    5. ___some college (at least one year)
    6. ___4-year college or university degree (Bachelor's degree)
    7. ___graduate degree (Master's or Doctorate)

7. Current or most recent occupation of PRIMARY CAREGIVER (Please list job title and describe position):

_____

8. Income (Please check the figure that best represents your gross yearly income):

___$0-4,999	___$5,000-$9,999	___$10,000-$14,999
___$15,000-$24,999	___$25,000-34,999	___$35,000-49,999
___$50,000-74,999	___$75,000-99,999	___$100,000 or more

Demographic Intake Form for Parents (Spanish)
Para Principal Responsible o Tutor
CONFIDENCIAL

Por favor NO escribe su nombre en esta forma.

1. ¿Cual es su relación con el adolescente que esta participando en este estudio?
   ____Madre ____Padre
   ____Abuela ____Abuelo
   ____Madrastra ____Padrastro
   ____Tía ____Tío
   ____Madrína ____Padríno
   ____Madre Adoptiva (Foster) ____Padre Adoptivo (Foster)
   ____Otro (explique)_____

2. ¿Cuál es la fecha de su nacimiento (mm/dd/aa) ¿Qué edad tiene Ud.? _____

3. ¿Cuál es su sexo? ____Masculino ____Femenino

4. ¿En que país nacío?
   ____México ____Estados Unidos ____Otro país (¿cual?)_____

5. ¿Cuánto tiempo ha vivido en Estados Unidos? _____

6. Marque el mas alto nivel educacional que ha terminado:
   1. ___sexto grado o menos
   2. ___secundaria (9° grado)
   3. ___parte de la preparatoria (10° al 11° grados)
   4. ___preparatoria o G.E.D.
   5. ___cuando menos un año de universidad
   6. ___ 4 años de universidad (licenciatura)
   7. ___postgrado (Maestría o Doctorado)

7. Su ocupación actual o la mas reciente de PADRE PRINCIPAL (Por favor describa su titulo y responsabilidades):
   _____

8. Salario (Por favor marque la cantidad que mejor represente su sueldo anual antes de pagar impuestos):
   ___$0-4,999 ___$5,000-$9,999 ___$10,000-$14,999
   ___$15,000-$24,999 ___$25,000-34,999 ___$35,000-49,999
   ___$50,000-74,999 ___$75,000-99,999 ___$100,000 o mas

References

Achenbach, T. M., & Edelbrock, C. (1983). *Manual for the Child Behavior Checklist and Revised Child Behavior Profile*. Burlington, VT: University Associates in Psychiatry.

Anderson, F. S., & Kunin Batson, A. S. (2009). Neurocognitive late effects of chemotherapy in children: The past 10 years of research on brain structure and function. *Pediatric Blood and Cancer 52*, 159-164.

Armstrong, F. D., & Mulhern, R. K. (1999). Acute lymphoblastic leukemia and brain tumors. In Brown, R. T. (Ed.), *Cognitive aspects of chronic illness in children*. New York: The Guilford Press.

Armstrong, D. F., & Reaman, G. H. (2005). Psychological research in childhood cancer: The Children's Oncology Group perspective. *Journal of Pediatric Oncology 30*(1), 89-97.

Barakat, L., Kazak, A., Meadows, A. et al. (1997). Families surviving childhood cancer: A comparison of posttraumatic stress symptoms with families of healthy children. *Journal of Pediatric Psychology, 22*, 843-859.

Barnes, Y. J. & Harvey, J. (2006). Long-term follow-up helps cancer survivors. Children's Hospital, St. Louis. Retrieved from http://www.stlouischildrens.org/tabid/159/itemid/3794/LongTerm-FollowUpHelps-Cancer-Survivors.aspx

Bauld, C., Anderson, V., & Arnold, J. (1998). Psychosocial aspects of adolescent cancer survival. *Journal of Pediatric Child Health, 34*, 120-126.

Bennett, D. S. (1994). Depression among children with chronic medical problems: a meta-analysis. *Journal of Pediatric Psychology, 19*, 149–170.

Berry, J. W., Kim, U., Minde, T. & Mok, D. (1987). Comparative studies of

acculturative stress. *International migration review, 21*(3), 491-511.

Brown, R., Kaslow, N., Hazzard, A., Madan-Swain, A., Sexson, S., Lambert, R., & Baldwin, K. (1992). Psychiatric and family functioning in children with leukemia and their parents. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*,495-502.

Bull, B. A. & Dorotar, D. (1991). Coping with cancer in remission: Stressors and strategies reported by children and adolescents. *Journal of Pediatric Psychology, 16*(6), 767-782.

Buizer, A.I., de Sonneville, L.M., den Heuvel-Eibrink M.M. & Veerman, A.J. (2006). Behavioral and educational limitations after chemotherapy for childhood acute lymphoblastic leukemia or Wilms tumor. *Cancer 106*, 2067–2075.

Burgess A.W. (1985). Sexual victimization of adolescents. In A.W. Burgess (Ed.) *Rape and sexual assault: A research handbook*. New York: Garland.

Butler, R., Hill, J. M., Steinherz, P. G., et al. (1994). Neuropsychologic effects of cranial radiation, intrathecal methotrexate, and systemic methotrexate in childhood cancer. *Journal of Clinical Oncology, 12*, 2621-2629.

Canning, E. H., Hanser, S. B., Shade, K. A. & Boyce, W. T. (1992). Mental disorders in chronically ill children: parent-child discrepancy and physician identification. *Pediatrics, 90*, 692–696.

Carey, R. C. (1974). Emotional adjustment in terminal patients: A quantitative approach. *Journal of Counseling Psychology, 21*, 433-439.

Carver, C. S., Scheier, M. F., & Weintraub, J. K. (1989). Assessing coping strategies: A theoretically based approach. *Journal of Personality and Social Psychology, 56*(2), 267-283.

Challinor, J. M. (1998). Behavioral performance of children with cancer: Assessment

using the Behavioral Assessment System for Children (Doctoral dissertation, University of California, San Francisco, 1998). Dissertation Abstracts International, 58 (12-B), 6484.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*. Lawrence Erlbaum, Hillsdale, New Jersey.

Compas, B. E., (1987). Coping with stress during childhood and adolescent. *Psychological Bulletin, 101*(3), 393-403.

Compas, B. E., Banez, G. A., Malcarne, V. & Worsham, N. (1991). Perceived control and coping with stress: A developmental perspective. *Journal of Social Issues, 47*(4), 23-34.

Copeland D.R., Moore B.D., Francis D.J., Jaffe N. & Culbert S.J. Neuropsychologic effects of chemotherapy on children with cancer: A longitudinal study. *Journal of Clinical Oncology, 14*, 2826-2835.

Daly, B. P., Kral, M. C., & Brown, R. T. (2008). Cognitive and academic problems associated with childhood cancers and sickle cell disease. *School Psychology Quarterly, 23*(2), 230-242.

Davis, P. C., Hoffman, J. C., Pearl, G. S. & Braun, I. F. (1986). CT evaluation of effects of cranial radiation therapy in children. *American Journal of Roentgenology, 147,* 587-592.

Deasy-Spinetta, P. (1981). The school and the child with cancer. In Spinetta, J.J., Deasy-Spinetta P, (Eds.) *Living with Childhood Cancer*. St Louis, MO: CV Mosby Company

Decker, C. L. (2006). Coping in adolescents with cancer: A review of the literature. *Journal of Psychosocial Oncology, 24*(4), 123-140.

Diagnostic and statistical manual of mental disorders (DSM-IV). (1994). Washington, D.C.: American Psychiatric Association.

Dolgin, M. J., Katz, E. R., Zeltzer, L. K. & Landsverk, J. (1989). Behavioral distress in pediatric patients with cancer receiving chemotherapy. *Pediatrics, 84,* 103–110.

Duffner, P. K., Cohen, M. E., Myers, M. H. & Heise, H. W. (1990). Survival of children with brain tumors: SEER Program, 1973-1980. *Neurology, 36,* 597-601.

Duffner, P. K., Horowitz, M. E., Krischer, J. P., Friedman, H. S., Burger, P. C., Cohen, M. E. et al. (1993). Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. *The New England Journal of Medicine, (328)*24, 1725-1731.

Eisen, A. R. (2007). *Treating childhood behavioral and emotional problems.* New York: Guilford Press

Ellenberg, L., McComb, J. G., Siegel, S. E. & Stowe, S. (1987). Factors affecting intellectual outcome in pediatric brain tumor patients. *Neurosurgery, 21,* 638-644.

Evans, A. E., Jenkin, D. T., Sposto, R., et al. (1990). The treatment of medulloblastoma: r results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone. *Journal of Neurosurgery, 72,* 572-582.

Faul, F., Erdfelder, E., Lang, A. G. & Buchner, A. (in press). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*.

Folkman, S. (1984). Personal control and stress and coping processes. *Journal of Personality and Social Psychology, 46*, 839-852.

Filley, C.M. (1999). Toxic Leukoencephalopathy. *Clinical Neuropharmacology 22,*(5), 249-260.

Filley, C.M., & Kleinschmidt-DeMasters, B.K. (2001). Toxic Leukoencephalopathy. *New England Journal of Medicine, 345,*(6), 425-432.

Fritz, G., Williams, J., & Amylon, M. (1988). After treatment ends: Psychosocial sequelae in pediatric cancer survivors. *American Journal of Orthopsychiatry, 58,* 552-561.

Geschwind, D. H., Loginov, M., Stern, J. M. (1999). Identification of a locus on chromosome 14q for idiopathic basal ganglia calcification (Fahr disease). *American Journal of Human Genetics, 65,* 764–72.

Greenberg, H., Kazak, A., & Meadows, A. (1989). Psychological adjustment in 8 to 16 year old cancer survivors and their parents. *Journal of Pediatrics, 114,* 488-493.

Hamburg, D. A. & Takinishi, R. (1989). Preparing for life: the critical transition of adolescence. *American Psychologist, 44*(5), 825-827.

Herbert Irving Comprehensive Cancer Center. (n. d.). Bone marrow transplant. Retrieved August 1, 2008 from, http://cpmcnet.columbia.edu/dept/medicine/bonemarrow/bmtinfo.html

Hollingshead, A. B. & Redlich, F. C. (1958). *Social class and mental illness*. New York: John Wiley.

Hobbie, W.L., Stuber. M., Meeske, K., Wissler, K., Rourke, M.T., Ruccione, K., Hinkle, A. & Kazak, A.E. (2000). Symptoms of posttraumatic stress in young adult survivors of childhood cancer. *Journal of Clinical Oncology, 18*, 4060–4066.

Jans, L., Stoddard, S. & Kraus, L. (2004). *Chartbook on Mental Health and Disability in the United States. An InfoUse Report.* Washington, D.C.: U.S. Department of Education, National Institute on Disability and Rehabilitation Research.

Kashani, J.& Hakami, N. (1982). Depression in children and adolescents with malignancy. *Canadian Journal of Psychiatry, 27,* 474–477.

Katz, E. R., Rubinstein, C. L., Hubert, N. C. & Blew, A. (1988). School and social reintegration of children with cancer. *Journal of Psychosocial Oncology, 6,* 123–140.

Kazak, A. E., Meeske, K., Penati, B., Barakat, L. P., Christakis, D., Meadows, A. T., Casey, R., & Stuber, M. (1997). Posttraumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. *Journal of Consulting and Clinical Psychology, 65*, 120-129.

Kazak, A. E., Christakis, D., Alderfer, M., & Coiro, M. J. (1994). Young adolescent cancer survivors and their parents: Adjustment, learning problems, and gender. *Journal of Family Psychology, 8,* 74-84.

Kazak, A. E., Stuber, M. L, Barakat, L. P, et al. (1998). Predicting posttraumatic stress symptoms in mothers and fathers of survivors of childhood cancer. *Journal of the American Academy of Child and Adolescent Psychiatry, 37*, 823-831.

Koocher, G. P. (1984). Terminal care and survivorship in pediatric chronic illness. *Clinical Psychology Review, 4,* 571-583.

Koocher, G.P., O'Malley, J.E., Gogan, J.L. & Foster, D.J. (1980). Psychological adjustment among pediatric cancer survivors. *Journal of Child Psychology and*

*Psychiatry and Allied Disciplines, (21)*1, 163-173.

Kingma, A., Mooyaart, E. L., Kamps, W. A., Nieuwenhuizen, P. & Wilmink, J. T. (1993). Magnetic resonance imaging of the brain and neuropsychological evaluation in children treated for acute lymphoblastic leukemia at a young age. *American Journal of Pediatric Hematology/Oncology, 15,* 231-238.

Kulka, R., Schlenger, W., Fairbank, J., Hough, R., Jordon, B. Marmar, C., & Weiss, D. (1990). *Trauma and the Vietnam War generation.* New York: Brunner/Mazel.

Lansky, S.B., List, M.A., & Ritter-Sterr, C. (1986). Psychological consequences of cure. *Cancer, 58,* 529-533.

Larcombe, I. J., Walker, J., Charlton, A., Meller, S., Jones, P. M. & Mott, M. G. (1991). Impact of childhood cancer on return to normal schooling. *BMJ, 301,* 169–171.

Leukemia and Lymphoma Society. (2010). Leukemia facts and statistics. In Leukemia facts and statistics. Retrieved November 17, 2010, from http://www.leukemia-lymphoma.org/all_page.adp?item_id=9346.

Liang, H., Chiang, Y., Chien, L. & Yeh, C. (2008) A comparison of emotional/behavioural problems between Taiwanese children with cancer and healthy controls. *Journal of Clinical Nursing, 17*(3), 304-311.

Lockwood, K. A., Bell, T. S. & Colegrove, R. W. (1999). Long-term effects of cranial radiation therapy on attention functioning in survivors of childhood leukemia. *Journal of Pediatric Psychology, 24*, 55-66.

Lo Nigro, L., Di Cataldo, A. & Schiliro, G. (2000). Acute neurotoxicity in children with

B-lineage acute lymphoblastic leukemia (B-ALL) treated with intermediate risk protocols. *Medical and Pediatric Oncology, 35,* 449–455.

Mahoney, D. H., Shuster, J. J., Nitschke, R., et al. (1998). Acute neurotoxicity in children with B-precursor acute lymphoid leukemia: an association with intermediate-dose intravenous methotrexate and intrathecal triple therapy: a Pediatric Oncology Group study. *Journal of Clinical* Oncology, *16,* 1712–1722.

Manyam, B. V., Walters, A. S., & Narla K. R. (2001). Bilateral striopallidodentate calcinosis: clinical characteristics of patients seen in a registry. *Movement Disorders, 16,* 258-64.

Masten, A.S., & Garmezy, N. (1985). Risk, vulnerability, and protective factors in developmental psychopathology. In B.B. Lakey & A.E. Kazden (Eds.), *Advances in clinical child psychology.* New York: Plenum.

Meister, L., & Meadows, A. (1993). Late effects of childhood cancer treatment. *Current Problems in Pediatrics, 23,* 102-131.

McDougal, S. (1997, December 11). Children with cancer; effects and educational implications. Retrieved July 13, 2008, from Pediatric Oncology Resource Center Web site: http://www.acor.org/pedonc/cfissues/backtoschool/cwc.html.

Miller, R. E. (2007). *Childhood cancer: Leukemia.* Retrieved July 31, 2008 from, http://kidshealth.org/parent/medical/cancer/cancer_leukemia.html.

Mulhern, R. K., Wasserman, A. L., Friedman, A. G. & Fairclough, D. (1989). Social competence and behavioral adjustment of children who are long-term survivors of cancer. *Pediatrics, 83*, 18–25.

Mulhern, R. K. & Palmer, S. L. (2003). Neurocognitive late effects in pediatric cancer. *Current Problems in Cancer, 27*(4), 177-197.

Mulhern, R. K. & Butler, R. W. (2005). Neurocognitive interventions for children and adolescents surviving cancer. *Journal of Pediatric Psychology (30)*1, 65-78.

National Childhood Cancer Foundation. (2008). *CureSearch*. Retrieved July 14, 2008, from, http://www.curesearch.org/about_us/index.aspx.

National Cancer Institute. (2008a). *Cancer: questions and answers.* Retrieved July 30, 2008, from http://www.nci.nih.gov/cancertopics/factsheet/Sites-Types/general

National Cancer Institute. (2008b). *Childhood cancers: questions and answers*. Retrieved July 30, 2008 from http://www.cancer.gov/cancertopics/factsheet/Sites-types/childhood

National Cancer Institute. (2008c). *Acute lymphoblastic leukemia in children.* Retrieved July 31, 2008 from http://www.nci.nih.gov/cancertopics/factsheet/ALLinchildren

National Cancer Institute. (2008d). *Adult acute myeloid leukemia treatment.* Retrieved July 31, 2008, from http://www.nci.nih.gov/cancertopics/pdq/treatment/adultAML/patient

National Cancer Institute. (2008e). *Childhood acute lymphoblastic leukemia treatment.* Retrieved July 31, 2008 from, http://www.nci.nih.gov/cancertopics/pdq/treatment/childALL/patient

Noll, R. B., Gartstein, M. A., Vannatta, K., Correll, J., Bukowski, W. M. & Davies, W. H. (1999). Social, emotional and behavioral functioning of children with cancer. *Pediatrics, 103*, 71-78.

Novakovic, B., Fears, T. R., Wexler, L. H., McClure, L. L., Wilson, D. L., McCalla, J. L. & Tucker, M. A. (1996). Experiences of cancer in children and adolescents. *Cancer Nursing, 19*, 54–59.

Peck, B. (1979). Effects of childhood cancer on long-term survivors and their families. *British Medical Journal, 1*, 1327-1329.

Pelcovitz, D., Libov, B. G., Mandel, F., Kaplan, S., Weinblatt, M., & Septimus, A. (1998). Posttraumatic stress disorder and family functioning in adolescent cancer. *Journal of Traumatic Stress, 11*(2), 205-221.

Price, R. A. (1983). Therapy related central nervous system diseases in children with acute lymphocytic leukemia. In Mastrangelo, R., Poplack, D. G., & Riccardi, R. (Eds.), *Central Nervous System Leukemia*: Martinus Nijhoff Publishers.

Pui, C. H. (2000). Acute lymphoblastic leukemia. In R. G. Steen and J. Mirro (Eds.). *Childhood Cancer: A handbook from St. Jude children's research hospital.* Cambridge, Massachusetts: Perseus Publishing.

Reynolds, C. R. & Kamphaus, R. W. (1992). *BASC - Behavioral assessment system for children: Manual.* Circle Pines, MN: American Guidance Service.

Reynolds, C. R. & Kamphaus, R. W. (2004). *Behavior assessment system for children, second edition (BASC-2): Manual*. Bloomington, MN: Pearson Assessments.

Reynolds, C. R. & Kamphaus, R. W. (2005). An advanced workshop on the BASC-2. Workshop given at the NASP 2005 annual convention, Atlanta, GA.

Ries, L. A., Miller, B. A. & Hankey, B. F. (Eds.). (1994). *SEER cancer statistic review 1973-1991: Tables and graphs (DHHS Publication No. NIH-2789).* Bethesda,

MD: National Cancer Institute, SEER Program.

Ries, L. A., Smith, M. A., Gurney, J. G. , Linet, M., Tamra, T., Young, J. L. & Bunin, G. R. (Eds). (1999). *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995, NIH Pub. No. 99-4649.* Bethesda, MD: National Cancer Institute, SEER Program.

Schiffer, R. B., Rao, S. M. & Fogel, B. S. (2003). *Neuropsychiatry: A comprehensive textbook.* Lubbock, Texas: Lippincott Williams & Wilkins.

Schwartz, C. L. (1999). Late effects of childhood cancer treatment. *The Oncologist, (4),*45-54.

Scott, R. & Howard, A. (1970). *Social stress: Models of stress.* Chicago, IL; Aldine.

Seligman, M. E. P. (1975). *Helplessness: On Depression, Development, and Death.* San Francisco: W.H. Freeman.

Seligman, M.E.P. and Maier, S.F. (1967). Failure to escape traumatic shock. Journal of *Experimental Psychology, 74,* 1–9.

Shalet, S. M., Gibson, B., Swindell, R. & Pearson, D. (1987). Effect of spinal radiation on growth. *Archives of Disease in Childhood, 62,* 461-464.

Shelby, M. D., Nagle, R. J., Barnett-Gueen, L. L., Quattlebaum, P. D. & Wuori, D.F. (1998). Parental reports of psychosocial adjustment and social competence in child survivors of acute lymphocytic leukemia. *Children's Health Care, 27*(2), 113-129.

Shelby, M. D. (1999). Risk and resistance factors affecting the psychosocial adjustment

of child survivors of cancer (Doctoral dissertation, University of South Carolina). *Dissertation Abstracts International, 59* (7-B), 3740.

Smith, M., Arthur, D., Camitta, Carroll, A.J., Crist, W., Gaynon, P., Gelber, R., et. al (1996). Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. Journal of Clinical Oncology 14, 18-24

Sorgen, K. E. & Manne, S. L. (2002). Coping in Children With Cancer: Examining the Goodness-of-Fit Hypothesis. Children's Health Care, 31 (3), 191-207. Retrieved August 08, 2008, from http://www.informaworld.com/10.1207/S15326888CHC3103_2

Spunberg, J. J., Chang, C. H., Goldman, M., Auricchio, E. & Bell, J. J. (1981). Quality of long-term survival following radiation for intracranial tumors in children under the age of two. *International Journal of Radiation Oncology Biology Physics, 7,* 727-736.

Stehbens, J. A., Kaleita, T. A., Noll, R. B., et al. (1991). CNS prophylaxis of childhood leukemia: What are the long-term neurological, neuropsychological and behavioral effects? *Neuropsychology Review, 2*(2), 147-177.

Stuber, M. L, Kazak, A. E., Meeske, K., et al (1997). Predictors of posttraumatic stress symptoms in childhood cancer survivors. *Pediatrics, 100*, 958-964.

Suc, E., Kalifa, C., Brauner, R., et al. (1990). Brain tumors under the age of three: the price of survival: a retrospective study of 20 long-term survivors. *Acta Neurochirurgica, 106*, 93-98.

Von der Weid, N., Mosimann, I., Hirt, A., et al. (2003). Intellectual outcome in children and adolescents with acute lymphoblastic leukemia treated with chemotherapy alone: Age- and sex-related differences. *European Journal of Cancer, 39,* 359 – 365.

Von der Kolk, B.A. (1985). Adolescent vulnerability to posttraumatic stress disorder. *Pychiatry, 48,* 365-370.

Verrill, J. R., Schafer, J., Vannatta, K. & Noll R. B. (2000). Aggression, antisocial behavior and substance abuse in survivors of pediatric cancer: possible protective effects of cancer and its treatment. *Journal of Pediatric Psychology, 25*, 493–502.

Waber D. P., Tarbell N. J., Kahn C. M., Gelber R. D. & Sallan S. E. (1992). The relationship of sex and treatment modality to neuropsychologic outcome in childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology, 10,* 810-817.

Waber, D. P. & Mullenix, P. J. (2000). Acute Lymphoblastic Leukemia. In Yeates, K.O., Ris, M.D., & Taylor H. G. (Eds.), *Pediatric Neuropsychology: Research, theory and practice.* (pp. 300-319). New York.: Guilford Press.

Weidman-Gibbs, H. & Acterberg-Lawlis, J. (1978). Spiritual values and death anxiety: Implications for counseling with terminal cancer patients. *Journal of Counseling Psychology, 25*, 563-569.

Wertlieb, D., Weigel, C.,&Feinstein, M. (1987). Measuring children's coping. *American Journal of Orthopsychiatry, 57*, 548-560.

Zeitlin, S. (1985). *Coping Inventory: A measure of adaptive behavior*. Bensenville, IL: Scholastic Testing Service.