

IMPACT OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA
AND ITS TREATMENT
ON SOCIAL-EMOTIONAL, INTELLECTUAL, AND ACADEMIC ABILITIES

By

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ABSTRACT

The occurrence of psychological late effects resulting from the diagnosis and treatment of pediatric acute lymphoblastic leukemia (ALL) been the subject of empirical investigations for approximately 25 years, with an emphasis on those patients treated with radiation therapy. In more recent years, however, research has shown that children and adolescents with ALL treated only with chemotherapy may also be at risk for treatment-related cognitive and academic deficits, although many specific treatment regimens remain to be investigated. *Purpose:* The present investigation was designed to examine 76 pediatric patients with ALL who were randomized to receive 1g/m² or 2g/m² of intravenous methotrexate (IVMTX) with regard to cognitive, academic, and social-emotional/behavioral functioning over a 3-year period beginning shortly after diagnosis. *Method:* Scores from a preexisting database were analyzed with particular interest in main effects for methotrexate dose level, time since diagnosis, age at diagnosis, ALL vs non-ALL status and interactions between group and time variables. Participants with ALL and group of non-ALL siblings had participated in cognitive evaluations measuring performance in the following domains: intelligence, language, visual-spatial/visual-motor skills, attention and working memory, processing speed, psychomotor speed and coordination, executive function, academic achievement, and social-emotional/behavioral functioning. *Results:* A main effect for methotrexate dose level was significant for a measure of adaptive skills. A main effect for age at diagnosis was noted on measures of visual-spatial attention and working memory, and spelling and written expression. No main effect for time was noted on any dependent measure. Additionally, no main effect

for ALL versus non-ALL status was noted on any dependent measure. *Conclusion:*

Overall the findings suggest that the treatment of ALL with $1\text{g}/\text{m}^2$ or $2\text{g}/\text{m}^2$ IVMTX does not significantly impact the incidence of late effects with regard to cognitive, academic, and social-emotional/behavioral functioning within the first 3 years post-diagnosis.

Younger age at diagnosis may, however, contribute to differences in performance on measures of cognitive and academic functioning.

CHAPTER 1

INTRODUCTION

Pediatric cancer and its treatment have been under investigation for centuries and more recently, advances in treatment have provided for vastly improved survival rates of children and adolescents with various types of pediatric cancer (American Cancer Society [ACS], 2008). For acute lymphoblastic leukemia (ALL), the most prevalent type of pediatric cancer (National Cancer Institute [NCI], 2007b), recent 5-year disease-free survival rate statistics have been observed at 80% (Roll, 2004). With increasingly successful medical treatment, more child and adolescent survivors of ALL are returning to their regular daily activities. However, research supports the changes in the cognitive, academic, and social-emotional/behavioral functioning of these survivors compared to their premorbid skills (Kadan-Lottick & Neglia, 2005). The challenge has been to identify specific treatment protocols that predispose children and adolescents with ALL to deleterious effects in these areas of functioning as the result of their illness and its treatment and individual characteristics that may mediate or moderate such treatment effects. Some survivors may, for example, experience impairments in academic achievement similar to those found in children with learning disabilities (Powers, Vannatti, Noll, Cool, & Stehbens, 1995). Historically, it was believed that only radiation therapy resulted in decrements in cognitive and academic performance among survivors of ALL (Kadan-Lottick & Neglia, 2005) and, thus, radiation is now typically reserved for cases of central nervous system (CNS) relapse or for very high-risk disease (Mulhern, Phipps, & White, 2004). Current research has shown that children and adolescents with

ALL who are treated only with chemotherapy may also be at risk for similar treatment-related cognitive and academic deficits (Kadan-Lottick & Neglia, 2005).

Studies that have examined social-emotional or behavioral functioning in pediatric survivors of ALL have concluded that behavioral difficulties may exist, specifically within the realms of social relationships (e.g., Earle & Eiser, 2007), academic behavior (e.g., Raymond-Speden, Tripp, Lawrence, & Holdaway, 2000) and adaptive skills (e.g., Shelby, Nagle, Barnett-Queen, Quattlebaum, & Wuori, 1998). Studies that have focused on the intellectual and academic performance in child and adolescent survivors of ALL have obtained mixed results. When groups of pediatric ALL survivors have been evaluated beyond the first year of treatment, some studies have reported significant declines in intellectual and academic performance. For example, Raymond-Speden and colleagues (2000) found that pediatric patients surviving ALL performed significantly worse in various areas of intelligence and academic abilities compared to groups of both healthy youth and youth with chronic asthma.

Some investigations have used a longitudinal approach to study intellectual and academic late effects of pediatric ALL and its treatment and have demonstrated significant declines in performance for groups of pediatric ALL survivors (e.g., Andrews Espy et al., 2001). Other investigations, however, have supported the notion that intellectual and academic functioning in pediatric survivors of ALL does not vary significantly as a function of time since diagnosis or treatment (e.g., Brown, Sawyer, Antoniou, Toogood, & Rice, 1999).

Finally, neuropsychological functioning in pediatric survivors of ALL has received attention in the psychological literature. In this regard, specific areas of functioning that are thought to be detrimentally impacted by ALL and its treatment include memory (e.g., Hill, Ciesielski, Sethre-Hofstad, Duncan, & Lorenzi, 1997), perceptual-motor skills (e.g., Buizer, De Sonnevill, Van Den Heuvel-Eibrink, Njikiktjien, & Veerman, 2005), and verbal skills (e.g., Précourt, Lamothe, Lassonde, Sauerwein, & Moghrabi, 2002).

From the review of 15 years of research in the areas of cognitive, academic, and social-emotional/behavioral late effects of pediatric ALL and its treatment, several methodological issues exist in the current literature that lend support for continued investigation of the late effects of ALL and its treatment among pediatric patients. First, a number of studies include heterogeneous groups of participants with pediatric cancer and fail to account for the possible effects of these within-group differences (e.g., Brown et al., 1999; Raymond-Speden et al., 2000; Reinfjell, Lofstad, Veenstra, Vikan, & Diseth, 2007). This may occur for several reasons including: a) small sample sizes of patients with ALL warrant the inclusion of participants with other cancer diagnoses, and b) specific treatment protocols include small numbers of potential participants and are therefore combined for analyses. Additionally, study participants have varied with regard to age at diagnosis and treatment, time since diagnosis, and age at follow-up evaluations, but again, are often grouped together in order to maximize sample size. Second, there is great variability in the measures used to evaluate constructs such as intelligence, academic achievement, social-emotional or behavioral functioning, and

neuropsychological functioning. This variability makes it difficult to draw consistent conclusions about how individual pediatric survivors of ALL will perform on a specific measure. In the case of rating scales, Eiser, Hill, and Vance (2000) reported that few to no studies have collected data related to behavioral functioning from multiple rating sources (i.e., child self report, parent report, teacher report), using the same or co-normed rating scales. Finally, Boman (2007) encouraged future studies to employ longitudinal designs in the assessment of cognitive, academic, and social/emotional late effects in pediatric survivors of ALL. This may be of particular importance as some of the studies reviewed by this investigator failed to find significant group differences or changes in performance of pediatric ALL patients who were tested within the initial 12 months after diagnosis (e.g., MacLean et al., 1995). Furthermore, for those studies highlighting significant changes in functioning over time for pediatric survivors of ALL, the numerous methodological issues related to within-group variance, as discussed above, often prevent the derivation of specific variables that contribute to these decrements in performance.

Educational personnel are dealt a great challenge when asked to provide evidence-based intervention to these children (Cruce & Stinnett, 2006) when conclusive studies about their expected impairments are limited. Pediatric survivors of ALL who show significant declines in school performance can be provided special services under the Individuals with Disabilities Education Improvement Act (IDEIA, 2004) category of Other Health Impaired (Zins, Ponti, & Noll, 1998). Ideally, identification of cognitive changes occurring early on during the treatment of ALL could be proven reliable in predicting more substantial cognitive declines likely to occur later, even years after

treatment completion (Mulhern et al., 2004). Because children and adolescents surviving cancer may evidence a variety of social, behavioral, academic, and cognitive difficulties that were not present before the onset of their illness, psychological interventions may be necessary to facilitate the youth's return to academic and related social activities (Cruce & Stinnett, 2006), with difficulties in social skill areas being an equally important area of focus as are academic skill areas (Noll, Pawletko, & Sulzbacher, 1993; Powers et al., 1995).

Purpose of the Present Study and Research Questions

This study was intended to address the methodological issues discussed above through longitudinal examination of 76 pediatric patients with ALL who were treated only with chemotherapy with respect to their performance on standardized measures of cognitive, academic, and social-emotional/behavioral functioning. This study was designed to address several methodological issues that were noted to exist in the body of reviewed literature. First, this study's sample included participants with ALL who were randomly assigned to treatment with one of two standardized chemotherapy protocols, and a non-ALL sibling comparison group. Second, other within-group differences that were thought to potentially affect performance on dependent measures and skew the actual effects of ALL and its treatment, such as age at diagnosis, and maternal education level were accounted for in statistical analyses. Third, the domain of social-emotional/behavioral functioning, was measured in this investigation with co-normed child self-report and parent report forms. Finally, a longitudinal design was employed, and participants were evaluated using consistent measurement tools across the 4

assessment periods (with the exception of those instances where participant age warranted change from one measure of intellectual function to another over the course of the 3 years, based on measurement tool norms). Studies that employ longitudinal designs are some of the strongest empirically (Mulhern et al., 2004). To help in the areas of comparison groups and measures of pre-morbid functioning, studies frequently incorporate data obtained from siblings of youth with cancer, as was the case in the current study. Siblings are assumed to share many genetic and environmental influences on functioning and thus are considered to be a useful comparison group (Mertens & Yasui, 2005; Trautman et al., 1988). Even in the absence of standardized assessment data obtained prior to the diagnosis of ALL—which may be considered quite impossible to gather given the relative rarity of ALL, the lack of standardization in assessment data that may be obtained from school districts, and the fact that many children are diagnosed prior to attending school for the first time (Trautman et al., 1988)—those studies that can measure functioning across time through treatment and beyond can provide useful information on changes in a child’s or adolescent’s functioning. The results of this study are a useful addition to the existing literature regarding the cognitive, academic, and social-emotional/behavioral late effects of ALL and its treatment with chemotherapy in a population of youth and those specific variables that may contribute to performance in these domains.

In this study, the cognitive functioning domain was comprised of scores from standardized measures of global intelligence, language, visual-spatial/visual-motor skills, attention and working memory, processing speed, psychomotor speed and coordination,

and executive function. Specifically, global intelligence was measured using Full Scale IQ (FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ) scores from the *Wechsler Abbreviated Scale of Intelligence* (WASI; Wechsler, 1999) and the *Wechsler Preschool and Primary Scale of Intelligence—Revised* (WPPSI-R; Wechsler, 1989). Language function was measured by scores from the Vocabulary and Similarities subtests from the WASI (Wechsler, 1999)/WPPSI-R (Wechsler, 1989) and the *Peabody Picture Vocabulary Test—Third Edition* (PPVT-III; Dunn & Dunn, 1997). Visual-spatial/visual-motor skills were measured using scores from the *Developmental Test of Visual Motor Integration—Fourth Edition* (VMI; Beery, 1997), and the Block Design subtest from the WASI (Wechsler, 1999)/WPPSI-R (Wechsler, 1989). Attention and working memory were measured with scores from the Arithmetic subtest score from the WPPSI-R (Wechsler, 1989)/WISC-III (Wechsler, 1991), the Digit Span subtest score and Freedom from Distractibility Index (FDI) score from the WISC-III (Wechsler, 1991), and the Bead Memory and Memory for Sentences subtests from the *Stanford-Binet Intelligence Scales—Fourth Edition* (SB-IV; Thorndike, Hagen, & Sattler, 1986a). Processing speed was measured using scores from the Coding and Symbol Search subtests from the WISC-III (Wechsler, 1991), as well as the Processing Speed Index (PSI) score from the WISC-III. Psychomotor speed and coordination was measured using scores from the *Purdue Pegboard Test* (PPT; Tiffin, 1968). Executive function was evaluated using scores from the Similarities subtest score from the WASI (Wechsler, 1999)/WPPSI-R (Wechsler, 1989), the Matrix Reasoning subtest from the WASI (Wechsler, 1999), and the Behavior Regulation Index (BRI), Metacognition Index (MI), and Global Executive Composite

(GEC) scores from the *Behavior Rating Inventory of Executive Function* (BRIEF; Gioia, Isquith, Guy, & Kenworthy; 2000).

Scores from the academic achievement measures assessed functioning in the following academic domains: reading, spelling and writing, and mathematics. In this regard, academic achievement was measured with scores from the Letter-Word Identification, Dictation, Calculation, and Applied Problems subtests from the *Woodcock-Johnson Psychoeducational Battery—Revised, Tests of Achievement* (WJ-R ACH; Woodcock & Johnson, 1989).

Social-emotional/behavioral functioning was assessed from the perspective of both the parent and the participant (where age norms allowed), and measured by the Externalizing Problems, Internalizing Problems, Adaptive Skills, and Behavioral Symptoms Index scores from the *Behavior Assessment System for Children (BASC)—Parent Report Form* (PRF; Reynolds & Kamphaus, 1993) and by the Personal Adjustment, Clinical Maladjustment, School Maladjustment, and Emotional Symptoms Index scores from the *BASC—Self-Report of Personality* (SRP; Reynolds & Kamphaus, 1993).

The following overarching research questions were addressed in the current study:

1. Does the cognitive, academic, and social-emotional/behavioral functioning profile of children and adolescents treated for ALL with intravenous methotrexate (IVMTX) change over time?

2. Does the dose of IVMTX differentially impact the performance of children and adolescents with ALL on measures of cognitive, academic, and social-emotional/behavioral functioning?
3. Do children and adolescents with ALL differ from a comparison group of non-ALL siblings on measures of cognitive, academic, and social-emotional/behavioral functioning over time?

The following null hypotheses were tested at the 0.05 alpha level with an *a priori* Bonferroni correction applied according to the number of dependent variables being tested for each domain of functioning. Thus the alpha level was reduced to either 0.025, 0.017, 0.013, or 0.01 for each of the following hypotheses:

1. Hypothesis I: Participants with ALL will not differ significantly over time as a function of methotrexate dose ($1\text{g}/\text{m}^2$ vs. $2\text{g}/\text{m}^2$ of IVMTX) on measures of global intelligence.
2. Hypothesis II: Participants with ALL will not differ significantly over time as a function of methotrexate dose on measures of language.
3. Hypothesis III: Participants with ALL will not differ significantly over time as a function of methotrexate dose on measures of visual-spatial/visual-motor skill.
4. Hypothesis IV: Participants with ALL will not differ significantly over time as a function of methotrexate dose on measures of attention and working memory.
5. Hypothesis V: Participants with ALL will not differ significantly over time as a function of methotrexate dose on measures of processing speed.

6. Hypothesis VI: Participants with ALL will not differ significantly over time as a function of methotrexate dose on measures of psychomotor speed and coordination.

7. Hypothesis VII: Participants with ALL will not differ significantly over time as a function of methotrexate dose on measures of executive function.

8. Hypothesis VIII: Participants with ALL will not differ significantly over time as a function of methotrexate dose on measures of academic achievement.

9. Hypothesis IX: Participants with ALL will not differ significantly over time as a function of methotrexate dose on measures of social-emotional/behavioral function.

10. Hypothesis X: Participants with ALL will not differ significantly over time as a function of age at diagnosis (< 5 years old vs. \geq 5 years old) on selected measures of cognitive, academic, and social-emotional/behavioral function.

11. Hypothesis XI: Participants with ALL will not differ significantly over time as compared to a group of healthy siblings on selected measures of cognitive, academic, and social-emotional/behavioral function.

CHAPTER 2

LITERATURE REVIEW

This section presents a review of relevant literature, beginning with a broad overview of childhood cancer and its 12 major subtypes. This general introduction is followed by an in-depth presentation of the literature examining the social-emotional, cognitive, and academic impact of ALL and its treatment on children and adolescents.

The empirical study of cancer and its treatment has been a major focus in the medical literature for centuries, although arguably, the most influential research has arisen only within the last century as a result of major advances in medical technology (American Cancer Society [ACS], 2008). Medical investigations have focused on a variety of aspects, such as the possible causes of cancer, effective treatment techniques, and late effects of the disease on physical health. As a result of such investigations, dramatically improved survival rates are now being observed in children and adolescents (Powers et al., 1995). In fact, despite the approximate 1,400 annual nationwide cancer-related deaths in individuals less than 15 years of age (Gurney & Bondy, 2006), mortality rates have declined in recent years to the point that over 80% of pediatric cancer survivors are disease free for 5 years and 75% of these survivors remain disease free for 10 years (National Cancer Institute [NCI], 2007; Smith & Gloeckler Ries, 2002). Research examining the impact of cancer treatments on these young survivors has been heavily focused on chemotherapy- and radiation therapy-related late effects. While constant modifications of treatment regimens warrant continued in-depth investigation, general findings indicate that children who are younger at the age of diagnosis and

treatment tend to suffer more health-related late effects, as well as those who are treated with radiation therapy (Brown & Madan-Swain, 1993; Mertens & Yasui, 2005). Medical research will likely continue for years to come, however, as many variables remain unexplored (Gurney & Bondy, 2006), and cancer continues to be the second most common cause of death in children (Diamond, 1998), and the leading cause of death by disease in children aged from infancy through 15 years (NCI, 2007a).

Childhood Cancer

Biology of Cancer

Cancer is a category of diseases grouped together by a common feature: the unregulated proliferation and interrupted maturation of cells. Malignant cells originate from one or more normal cells that are damaged at the genetic level (Workman, 2004). When a cell's DNA becomes damaged or altered it can no longer regulate the activities of that cell (American Cancer Society [ACS], 2008) and the cell subsequently loses its regular characteristics and/or begins to express abnormal characteristics (Workman, 2004). The cell's regulatory function can be impacted in two ways: a) suppressor genes, designed to inhibit growth, become deactivated or deleted, and/or b) oncogenes, which normally initiate cell growth and production (needed in normal cells for development or replacement of dead cells) (Workman, 2004), are stimulated at an inappropriate time (Steen, 2000b). These altered cells can become either benign (non-cancerous), malignant (cancerous) (Workman, 2004), or die. Cancerous cells divide repeatedly, increasing the number of abnormal cells present (ACS, 2008; Cruce & Stinnett, 2006; Friedenbergs, Grunwald, & Kaplan, 2005; Li & Wendt, 1998) and causing damage to healthy tissue (Li

& Wendt, 1998) through a “loss of normal cell organization” (Steen, 2000b). Cancer may appear as a tumor or solid mass of malformed cells in fluid systems (e.g., circulatory or lymphatic), or in the bone marrow (ACS, 2008; Cruce & Stinnett, 2006). Malignant cells can be distinguished from normal cells based on a number of differences in appearance and functioning. More specifically, cancerous cells have larger and irregularly shaped nuclei, may be missing part or all of certain chromosomes, and are functionally useless. Additionally, they have an abnormally increased rate of cell division and this process is continuous. Cancerous cells also fail to adhere to neighboring cells in a normal fashion, which allows for metastasis (Workman, 2004).

Cancerous cells can spread via two methods. Invasion, an active method of local spread, occurs when cancerous tumor penetrates surrounding areas of the body by sending out projections of cancerous cells, which have the capacity to form other malignant tumors (Steen, 2000a). Metastasis, or passive spread via the blood or lymph fluid (ACS, 2008; Friedenbergs et al., 2005), is a method by which cancerous cells reach distal locations in the body (Steen, 2000a). The degree of spread is an important prognostic factor (Steen, 2000b).

There are over 100 different types of cancer (Cruce & Stinnett, 2006; Friedenbergs et al., 2005; Li & Wendt, 1998) that can impact individuals across the lifespan. Steen (2000b) noted that there are several major differences, however, between those cancers typically diagnosed in childhood and those typically diagnosed during adulthood. Childhood cancers tend to have higher cure rates, which may in part be due to the fact that children are generally more resilient through the aggressive cancer treatment

procedures. Additionally, the type of cells impacted by childhood cancers are more often undifferentiated stem cells, whereas in adult cancers the cells affected are more differentiated. Additionally, while cancer in both pediatric and adult populations results from cell damage at the level of DNA, the causes of this damage vary by population. In childhood cancers cellular damage generally result from genetic causes and from gene-environment interactions, rather than the environmental causes that usually initiate adult cancers (i.e. exposure to toxins) (Roll, 2004; Steen, 2000b). Despite the genetic etiology of childhood cancers, less than 5% of these diseases are inherited (ACS, 2008; Reardon, 2000). The specific etiology of most cancers is uncertain, although they are each likely due to a complex interaction of biological and environmental variables (Friedenbergs et al., 2005; Li & Wendt, 1998) that results in “genetic accidents.” There are a number of risk factors that have been linked to the development of specific types of cancer (ACS, 2008).

Prevalence and Incidence of Pediatric Cancers

As previously mentioned, cancer occurs throughout the lifespan, although some types are more prevalent in specific age groups. On the whole, childhood cancers are much less prevalent than are adult malignancies, with 238,000 children aged birth to 19 years having cancer in the year 2004 (ACS, 2008). This incidence of childhood cancers represents less than 1% of all cancers reported by developed nations (Cruce & Stinnett, 2006). According to NCI statistics, an average of 150 out of every 1 million individuals under the age of 20 years will be diagnosed with cancer yearly, with incidence rates being highest in the 15 through 19 year age group as well as children under the age of 5 years

(as cited in Gloeckler Ries, Percy, & Bunin, 1999). Overall, 1 in every 7,000 children between the ages of 1 and 14 years in the United States is diagnosed annually with some type of cancer (Gurney & Bondy, 2006; Smith & Gloeckler Ries, 2002). This incidence level results in 1 of every 500 to 600 children being diagnosed with cancer by the time they reach the age of 15 years (Mirro, 2000). Despite the heterogeneity of childhood cancers, the majority of youth with cancer have one of the three most common subtypes, which include leukemias (32.6% of all childhood cancers), tumors of the central nervous system (CNS) (21.2% of all childhood cancers), and lymphomas (7.9% of all childhood cancers), respectively (Cruce & Stinnett, 2006; Steliarova-Foucher, Stiller, Lacour, & Kaatsch, 2005).

Diagnosis and Treatment of Pediatric Cancer

There are a variety of procedures used to diagnose childhood cancer. The discovery process usually includes a general physical exam and patient history. Minimally invasive procedures used include a urine test, blood tests, and neurological exam. More invasive procedures include immunohistochemistry (injecting dye or enzymes into the bloodstream), biopsy (the removal of tissues or cells for microscopic examination), and bone marrow aspiration (the removal of bone, bone marrow, and blood for microscopic examination) (e.g., NCI, 2007h). Several methods of scanning different regions of the body may also be used to identify the presence of cancer. These include x-ray, CT scan (use of an x-ray machine and computer to take pictures of a portion of the body from a variety of angles), ultrasound (a technique during which sound waves are bounced off organs in the body and the echoes create images) (e.g., NCI, 2007h), and

MRI (use of a magnet, radio waves, and a computer to create a detailed image of a portion of the body) (e.g., NCI, 2007f).

Once cancer is diagnosed in a patient, the medical team begins to plan the treatment procedures that will be used. The prognosis, or chances of survival, varies for each specific subtype of cancer and is contingent upon the assigned stage in addition to a number of variables, such as the patient's age and gender (Li & Wendt, 1998). Staging procedures, varying with the type of cancer, come from several sources, for example the *American Joint Committee on Cancer Staging Manual* (AJCC; 2002), the *Children's Cancer Group* guidelines (Children's Cancer Group, 1991), and the *Pediatric Cancer Staging Guide* (Newton et al., 1993).

Standard treatment protocols vary with the type of cancer being targeted, the age of the patient, and the prognosis. Surgical procedures are fairly common in cancer treatment. They involve complete or partial removal of the malignant tumor and often surrounding tissue (e.g., NCI, 2007h; 2007i; 2007k). Other surgical alternatives involve organ transplants, such as the liver, or bone marrow transplants (Diamond, 1998; NCI, 2007f). Sometimes, radiation therapy is used in conjunction with surgery in an attempt to reduce the tumor size before its removal. Radiation therapy involves exposing the cancerous tissue to "high-energy" x-rays or other types of radiation. Radiation can be introduced into the body via an external machine or through injected radioactive material. Chemotherapy drugs (often a combination of multiple substances including alkylating agents, antimetabolites, antitumor antibiotics, plant alkaloids, corticosteroids, and L-asparaginase) are used to destroy dividing cells (Diamond, 1998). These drugs are

administered orally, intravenously, or intramuscularly, all of which achieve systemic treatment. When only regional treatment is needed, the chemotherapy drugs can be injected more directly into an organ, body cavity, or the spinal fluid (intrathecal chemotherapy). Chemotherapy with stem cell transplant combines high doses of chemotherapeutic agents with the replacement of healthy blood cells that were inadvertently destroyed along with the malignant cells. This is done through the use of stem cells extracted from blood or bone marrow (NCI, 2008a).

Major Types of Pediatric Cancer

Although childhood cancers represent an assorted group of diseases (Li & Wendt, 1998), these diseases can be grouped into 12 major categories as described in the *International Classification of Childhood Cancers, Third Edition* (Steliarova-Foucher et al., 2005). These categories of cancer in children vary based on cell structure, site of origin, and demographic factors (Gloeckler Ries et al., 1999).

Leukemias are cancers of the blood and bone marrow. Healthy bone marrow produces stem cells, which develop into the three types of cells found in the blood: red blood cells, white blood cells, and platelets. Each type of cell is essential for the body to function properly. Healthy red blood cells oxygenate the body; healthy white blood cells fight infection in the body; healthy platelets assist with clotting to prevent blood loss (NCI, 2007b; 2007c). Leukemias in children can be either acute or chronic, although chronic leukemias are rare in children (Diamond, 1998; NCI, 2007c), accounting for only 3% of childhood leukemias (Lanzkowsky, 2005). Within the classification of acute leukemias, they can be further subdivided into lymphoblastic (also known as

lymphocytic) or nonlymphoblastic (also known as myelogenous) (NCI, 2007b; 2007c). In ALL an unusually large number of lymphoblasts (an immature type of white blood cell) are formed from stem cells, although they do not possess the normal infection-fighting properties of mature lymphocytes. This overproduction of lymphoblasts also leads to overcrowding of regular blood cells, further interfering with their regular functioning (NCI, 2007b). In acute myelogenous leukemia (AML), another type of white blood cell, called myeloblasts, are produced. They too, fail to properly fight infection and overcrowd healthy blood cells, additionally impairing their functioning (NCI, 2007c). Leukemic cells spread throughout the body, via circulatory and lymphatic systems, often reaching the brain, spleen, and liver (Cruce & Stinnett, 2006; Zins et al., 1998). The result is a reduced capacity to fight infection, excessive bleeding, and anemia (Cruce & Stinnett, 2006). Other common symptoms of acute leukemia include fever, pain (NCI, 2007b; 2007c; Roll, 2004; Vietti & Steuber, 2002), fatigue, night sweats, shortness of breath, bruising, and skin changes, including lumps, rashes, and paleness (NCI, 2007b; 2007c; Roll, 2004).

Acute lymphoblastic leukemia is the most prominent type of cancer occurring in children less than 15 years of age in the United States (NCI, 2007b), and accounted for 23.6% of all childhood malignancies diagnosed between 1992 and 2001 (Gurney & Bondy, 2006). Lanzkowsky (2005) reported that leukemias as a whole account for up to 30% of childhood malignancies. Diagnosis of ALL is highest in the 2- to 5-year age group (Lanzkowsky, 2005); annual incidence rates reach 3,000 cases (Rytting, Choroszy, Petropoulos, & Wah Chan, 2005), or the equivalent of 3 to 4 cases per 100,000 Caucasian

children in the United States (Lanzkowsky, 2005). Males have higher incidence rates of ALL than do females (Smith & Gloeckler Ries, 2002). Acute myelogenous leukemia is also diagnosed more frequently in younger children (less than 5 years of age) and incidence rates are also slightly higher in the 15- to 19-year age group. This type of leukemia is more common in females (Smith, Gloeckler Ries, Gurney, & Ross, 1999).

Certain demographic groups have been identified as having higher risk of developing acute leukemia. Hispanic children are at greater risk for developing either ALL or AML (NCI, 2007b; 2007c). Hispanic and Caucasian children are also more likely to develop ALL, as compared to other racial groups (Gurney & Bondy, 2006; NCI, 2007b).

Biological risk factors for acute leukemia include conditions such as Down's syndrome, having a sibling with leukemia (NCI, 2007b; 2007c), Fanconi anemia, neurofibromatosis type 1, Noonan syndrome (NCI, 2007c), Poland syndrome, Diamond-Blackfan anemia, and Bloom syndrome (Lanzkowsky, 2005). Environmental risk factors for acute leukemia include exposure to radiation or certain chemicals (NCI, 2007b; 2007c; Roll, 2004), prenatal exposure to x-rays (NCI, 2007b), previous treatment with chemotherapy (NCI, 2007b; 2007c), and prenatal exposure to nicotine or alcohol (NCI, 2007c). However, direct causes of acute leukemia have yet to be identified (Roll, 2004).

Five-year survival rates for children with ALL range from 65% to 80% depending on the assigned risk level. In children with AML, survival rates range from 40% to 45% (Roll, 2004). Factors included in the determination of ALL risk level include patient age, white blood cell counts, subtype of ALL, the degree of metastasis to the central nervous

system, and the child's initial response to therapy. Those individuals with worse prognosis are younger than age 1 or older than age 10 at diagnosis, have high white blood cell counts, have metastatic leukemia found in the central nervous system, and do not respond well initially to therapy (Lanzkowsky, 2005).

Lymphomas, both Hodgkin and non-Hodgkin (NHL), are characterized by the development of malignant cells in the part of the immune system known as the lymph system. A healthy functioning lymph system is designed to fight infection through drainage, removal of germs, and transportation of infection-fighting white blood cells (Hudson, 2000). This system is vast and thus cancerous cells may develop in a number of areas. The lymph fluid, vessels, and nodes can be affected, as well as the spleen, thymus, tonsils and bone marrow. From these areas, malignant cells and tissue may spread throughout the body. Each type of lymphoma can be further differentiated into subtype based on the microscopic structure of the malignant cells (NCI, 2007e; NCI, 2008a; Sandlund, 2000). Symptoms of Hodgkin's lymphoma include swollen lymph nodes, fever, night sweats, weight loss (Hudson, 2000; NCI, 2008a), fatigue, anemia, and persistent itching (Hudson, 2000). Non-hodgkin's lymphoma may also result in swollen lymph nodes and breathing problems (NCI, 2007e), and depending on the subtype, pale skin and bruising, nausea, vomiting, pain, obstructed bowels, or abdominal, shoulder, or neck swelling (Sandlund, 2000).

Lymphomas are the third most common type of childhood cancer, with incidence rates reaching 1,700 in individuals less than 20 years of age; Hodgkin's lymphoma represents 850 to 900 of these cases (Percy, Smith, Linet, Gloecker Ries, & Friedman,

1999). Hodgkin's lymphoma is more prevalent in adolescents whereas NHL predominates in the younger age groups (Wah Chan, Petropoulos, Chang, and Rytting, 2005). Gender differences are also noted in Hodgkin's lymphoma prevalence rates with males dominating in younger age groups and the opposite trend noted in youth over 15 years of age (Percy et al., 1999). Males also predominate in cases of NHL for all individuals less than 15 years of age (Sandlund, 2000). With regard to racial differences, Caucasian children predominate in both subtypes (Percy et al., 1999). Risk factors for Hodgkin's lymphoma include genetic predisposition, as increased incidence rates are found among siblings, and having an immunological disorder, and/or Epstein-Barr virus (Hudson, 2000; Lanzkowsky, 2005). Risk factors for NHL include those associated with the incidence of Hodgkin's lymphoma, in addition to a suppressed immune system post-transplant, a history of radiation therapy, HIV/AIDS, and exposure to a drug known as diphenylhydantoin (Lanzkowsky, 2005, Sandlund, 2000).

Lymphomas are now considered to be a curable form of cancer (Wah Chan et al., 2005). Hodgkin's lymphoma has a higher 5-year survival rate than does NHL; these are 91% and 72%, respectively, for children less than 20 years of age (Percy et al., 1999). Hodgkin's lymphoma is divided into four stages, with stage 1 being the least aggressive or most localized form of cancer and stage 4 being the most aggressive and/or with metastatic disease. Non-hodgkin's lymphoma is similarly staged on a 1 to 4 scale. Most NHL tumors are aggressive; 30% of cases are unresponsive to initial treatment attempts and/or evidence recurrence (Sandlund, 2000).

Central nervous system (CNS) tumors and other neoplasms are malignant masses occurring in the brain and spinal cord. Central nervous system tumors are the second most common type of cancer diagnosed in children (Gurney & Bondy, 2006; Lanzkowsky, 2005). Childhood brain tumors are unique in that they are most frequently primary tumors (i.e., originate in the brain), whereas in adults, brain tumors more often result from cancer originating in another location that has spread to the CNS (Heideman & Havens, 2000). There are 100 different types of CNS tumors, with glial tumors being the most common (Heideman & Havens, 2000). Ninety percent of childhood CNS tumors originate within the brain (Gurney, Smith, & Bunin, 1999) and metastasis outside the CNS rarely occurs (Lanzkowsky, 2005). Specific types of tumors include astrocytomas, medulloblastomas, brain stem tumors, ependymomas, optic gliomas, craniopharyngiomas, and intracranial germ cell tumors (Lanzkowsky, 2005).

Astrocytomas are the most common type of glial tumor (approximately 50% of cases) in children (Lanzkowsky, 2005). Most CNS tumors in children (particularly those aged 9 years and younger) appear in the infratentorial region (including the lower portions of the brain between the foramen magnum and through the brainstem) (Gurney, Smith, et al., 1999; Lanzkowsky, 2005). In children aged 10 years and older, more CNS tumors originate in the cerebrum (Gurney, Smith, et al., 1999). Other CNS tumors can occur in the supratentorial region (or the cerebral hemispheres and diencephalon) (Lanzkowsky, 2005). The signs and symptoms of CNS tumors vary greatly based on the age of the child and the site of the tumor. Some general signs of intracranial tumors include headaches, seizures, those ailments associated with increased intracranial

pressure (e.g. vomiting, nausea, drowsiness, vision trouble, decreased levels of consciousness) (Ater, Wienberg, Maor, Moore, & Copeland, 2005; Roll, 2004), cranial nerve abnormalities, and disturbed gait or balance (Lanzkowsky, 2005). Young children with an intracranial tumor may show irritability, and/or developmental regression or delays (Ater et al., 2005). Older children may experience changes in their personality and school performance (Roll, 2004). Some of the common symptoms associated with spinal tumors are back pain, muscle spasms or weakness, gait disturbance, a reappearance of the positive Babinski reflex, and changes in reflex responses (Lanzkowsky, 2005). In general, areas of functioning that are usually controlled by specific parts of the brain are the functions impacted by tumors in those locations. For example, tumors in the cerebellar or brainstem region can negatively affect balance, coordination, and cranial nerves (Ater et al., 2005).

Approximately 35 cases per million are diagnosed each year in children from birth to 15 years of age in the United States (Lanzkowsky, 2005) and incidence rates decline with age (Gurney, Smith, et al., 1999). Tumors of the CNS have significantly higher incidence rates in Caucasians and males (Gurney, Smith, et al., 1999). With the use of current imaging technology (e.g., MRI, CT scans), more CNS tumors are diagnosed at earlier stages in children than ever before (Roll, 2004). Risk factors for CNS tumors include children having neurofibromatosis types 1 or 2 (Lanzkowsky, 2005; Roll, 2004), Tuberous sclerosis, von Hippel-Lindau syndrome, Li-Fraumeni syndrome, Turcot syndrome, Gorlin syndrome (Lanzkowsky, 2005) and those with bilateral retinoblastoma (Roll, 2004). Non-biological risk factors include exposure to radiation, or industrial or

chemical toxins (Roll, 2004). Overall survival rate is approximately 64%, with a degree of variability based on tumor location (Roll, 2004).

Neuroblastomas and other peripheral nervous system tumors are clusters of cancerous cells occurring in the nerve tissue of the adrenal glands, chest, neck, or spinal cord (NCI, 2007h; Roll, 2004). The two most common sites for neuroblastomas to originate are the abdomen (Lanzkowsky, 2005) and chest (Bowman, 2000). At the time of diagnosis, approximately 75% of cases are associated with significant spread of the cancerous cells to many other bodily systems including the lymph nodes, bones and bone marrow, liver, and skin (Bowman, 2000; NCI, 2007h). General symptoms include lethargy and/or weakness, pallor, anorexia, weight loss, abdominal pain, and irritability (Roll, 2004). More specific symptoms vary greatly based on the site of origin of the tumor; symptoms associated with an abdominal tumor (the most common site of origination) can include anorexia, vomiting, abdominal pain or mass, and liver problems (Lanzkowsky, 2005).

Neuroblastomas occur in 1 in 7,000 live births, with 90% of neuroblastomas being diagnosed by the time the child reaches the age of 10 years (Lanzkowsky, 2005). Each year, around 700 individuals younger than age 20 are diagnosed with a neuroblastoma (97% of cases) or other sympathetic nervous system tumor (Goodman, Gurney, Smith, & Olshan, 1999). Neuroblastomas are most commonly diagnosed in children less than 5 years of age (NCI, 2007h), with the median age of diagnosis being 2 years of age (Bowman, 2000; Diamond, 1998). Neuroblastomas are the most common type of pediatric cancer occurring in children less than 1 year of age (Goodman et al., 1999).

Prevalence rates are higher in males (Lanzkowsky, 2005). There are notable racial differences in incidence of this type of cancer during the first year of life. These differences, however, are not present in older age groups (Goodman et al., 1999). The cause(s) of neuroblastomas and other peripheral sympathetic nervous system tumors remain(s) largely unknown (Goodman et al., 1999; Roll, 2004). Prenatal and perinatal genetic mutations are the likely cause of this category of cancers (Ater & Worth, 2005); risk factors include neurofibromatosis type 1, Beckwith-Wiedemann syndrome, and nesidioblastosis, and prenatal exposure to specific anticonvulsants (Bowman, 2000).

The likelihood of curing neuroblastomas and other peripheral nervous system tumors varies based on the age at diagnosis, the tumor location, stage, risk level, and other tumor characteristics such as shape, function, cellular structure, level of cellular irregularity from non-cancerous cells, growth rate, and chromosomal levels. Staging of neuroblastomas involves a four-level system based on the degree of tumor metastasis and amount that can be surgically removed. Overall 5-year survival rates are approximately 57% (Gatta, Capocaccia, Coleman, Gloeckler Ries, & Berrino, 2002). Survival rates are higher in patients diagnosed before 1 year of age (83% survival rate), and decrease to 55% in cases where diagnosis occurs between ages 1 and 4 years, and to 40% for those children diagnosed at age 5 years and older (Goodman et al., 1999).

Retinoblastomas. In retinoblastoma, cancerous tissue forms in the retina of one or both eyes, although unilateral occurrence is more common (75% of cases; Roll, 2004). Bilateral retinoblastoma occurs because of two primary tumors, not as the result of spread from one eye to the other (Pratt, 2000b). There are two subtypes of retinoblastoma,

depending on where in the eye the cancer originates: exophytic and endophytic (Pratt, 2000b). The cancerous tissue is generally contained within the retina rather than spreading to other parts of the body as it does in other types of cancer (Lanzkowsky, 2005). However, in cases where spread does occur, it can reach tissue underneath the retina, the eye socket, forward to the front of the eye, or backward via the optic nerve and toward the brain (Pratt, 2000b). Common symptoms include swelling of the eye, unequal pupil size, change in eye color (Pratt, 2000b), a white appearance of the pupil in photographs, or deviation of the eye (Faustina, Herzog, & Gombos, 2005; Lanzkowsky, 2005).

Retinoblastoma is most common in children less than 5 years of age although it may appear at any age (NCI, 2007j). The median age of diagnosis for retinoblastoma is 18 months (Lanzkowsky, 2005). There are no significant gender and racial differences in the incidence rates (Young, Smith, Roffers, Liff, & Bunin, 1999). Approximately 200 to 350 new cases are diagnosed each year, or 1 in every 15,000 to 20,000 live births (Faustina et al., 2005; Lanzkowsky, 2005). Reports of cases that are considered inherited range from 10% (Faustina et al., 2005) to as many as 40% (Lanzkowsky, 2005). The identification of risk factors associated with retinoblastomas has received inconsistent support, and thus causes remain unknown (Lanzkowsky, 2005). Retinoblastoma is staged based on the degree of metastasis (NCI, 2007j). The 5-year survival rate for treated retinoblastoma is approximately 93% (Young, et al., 1999); retinoblastoma is almost always fatal if left untreated (Faustina et al., 2005).

Renal tumors refer to a group of cancers originating in the kidneys. The most common subtype of renal tumors is the Wilm's tumor (Bernstein, Linet, Smith, & Olshan, 1999; Lanzkowsky, 2005). Generally, these tumors appear only in a single kidney, although in cases where both kidneys are affected, it is due to the occurrence of two primary tumors rather than metastasis from one kidney to another (Dome, 2000). These tumors can metastasize to the lungs, liver, or regional lymph nodes (NCI, 2007k). The most common symptoms of this type of cancer are the presence of a mass in the abdomen (Jaffe & Pearson, 2005b; Lanzkowsky, 2005; Roll, 2004), blood in the urine, and unexplained fever (NCI, 2007k). Approximately 78% of Wilm's tumor cases are diagnosed before the child reaches age 5 (Bernstein, Linet, et al., 1999; Jaffe & Pearson, 2005b), with peak age of diagnosis between ages 2 and 4 years (Lanzkowsky, 2005; Roll, 2004). Annual incidence rates are approximately 1 in every 10,000 children in the United States under the age of 15 years (Lanzkowsky, 2005). No significant gender or racial group differences are noted (Bernstein, Linet, et al., 1999; Dome, 2000). Risk factors for Wilm's tumor include the following congenital anomalies: aniridia, Beckwith-Wiedemann syndrome, genitourinary malformations hemihypertrophy, and Denys-Drash syndrome (Jaffe & Pearson, 2005b; Lanzkowsky, 2005, Roll, 2004). However, direct causes of renal tumors are unknown (Jaffe & Pearson, 2005b). Renal tumors are staged according to the level of regional and distal spread of the tumor and the amount of tumor that can be successfully surgically removed (Lanzkowsky, 2005). Overall survival rates range from 81% to 95%, with variance due the stage of the tumor (Lanzkowsky, 2005), the individual's age, type and size of the tumor, tumor cell structure, and success of

surgical removal (NCI, 2007k). Five-year survival data related to children with Wilm's tumor is 90% (Gatta et al., 2002), with females and African American children having better chances of survival (Bernstein et al., 1999).

Hepatic tumors originate in the liver. The two most common subtypes include hepatoblastomas and hepatocellular carcinomas (Lanzkowsky, 2005). The most common symptom is the presence of a mass in the abdomen (Lanzkowsky, 2005), but other symptoms include vomiting, pain, diarrhea, fever, weight loss, and jaundice (Furman, 2000). These cancers are relatively rare in children (Furman, 2000). Of those 100 to 150 cases in childhood (Bulterys, Goodman, Smith, & Buckley, 1999), 90% are diagnosed prior to the child's third birthday (Furman, 2000; Lanzkowsky, 2005). Hepatoblastomas are more common in younger age groups, whereas hepatocellular carcinomas occur relatively evenly across the age groups (NCI, 2008b). However, in both subtypes, male gender is associated with an increased risk for developing the disease (NCI, 2008b). As with other types of childhood cancer, the specific causes of hepatic tumors remains unknown but the presence of various congenital anomalies have been identified risk factors. For hepatoblastomas, risk factors include hemihypertrophy, Beckwith-Wiedemann syndrome, being born without an adrenal gland or without a kidney, umbilical herniation (Lanzkowsky, 2005), and low birth weight (NCI, 2008b). For hepatocellular carcinomas, risk factors include hepatitis types B and C, and liver damage (NCI, 2008b). The staging of hepatic tumors is based upon the amount of tumor that can be successfully surgically removed and the presence of metastasis, with some sources reporting survival rates as high as 90% to 100% (Lanzkowsky, 2005). Other factors

affecting prognosis include the type of hepatic tumor and whether the cancer is reoccurring or a first time diagnosis (NCI, 2008b).

Malignant bone tumors occur when cancerous cells form within the bones (NCI, 2007i). The two most common types of malignant bone tumor are osteosarcoma and Ewing's sarcoma, with osteosarcoma having an incidence rate twice that of Ewing's sarcoma (Lanzkowsky, 2005). The most common site of origin for osteosarcomas is the knee (NCI, 2007i) or in areas of the body near growth plates (Pratt, 2000a), such as the distal femur, proximal tibia, and proximal humerus (Lanzkowsky, 2005; Roll, 2004). For Ewing's sarcoma, the most common sites of origination are the limbs, chest, trunk, or back (NCI, 2007g; Pappo & Pring, 2000b). Ewing's sarcoma forms in the soft tissue of the bone (NCI, 2007g). Common symptoms include pain at the tumor site, difficulty bearing weight (Roll, 2004), swelling, idiopathic fracture, and decreased range of motion (Lanzkowsky, 2005). These types of tumors are more common in patients 10 to 19 years of age (Lanzkowsky, 2005; Roll, 2004); likely due, in part, to the periods of rapid growth that occur in this older age group (Jaffe & Pearson, 2005a). Osteosarcomas are also more prevalent in males (Jaffe & Pearson, 2005a) and African Americans (Lanzkowsky, 2005). In the case of Ewing's sarcoma, the disease is less prevalent in African American and Asian American children (Lanzkowsky, 2005) although there is still a higher incidence in males (Herzog, Mahajan, & Lewis, 2005). These gender differences in incidence rates do not tend to appear until adolescence (Gurney, Swensen, & Bulterys, 1999). Some identified risk factors for bone tumors include: bilateral retinoblastoma, Li-Fraumeni syndrome, bone diseases, and a history of radiation therapy or chemotherapy

(Lanzkowsky, 2005). However, the specific causes of bone tumors remain largely unknown in most cases (Gurney, Swensen, et al., 1999; Roll, 2004). Overall survival rates from osteosarcomas are approximately 65%, with prognosis being heavily influenced by the presence of lung metastasis, the likelihood of success of tumor removal (Roll, 2004), the size and type of tumor, and the patient's age (NCI, 2007i). Five-year survival data for Ewing's sarcoma is approximately 61% (Gatta et al., 2002); in cases where the cancer has metastasized to other areas of the body, survival rates are reduced to between 10% and 40% (Lanzkowsky, 2005). No specific staging system for malignant bone tumors exists; they are classified simply based on whether or not the cancer has metastasized (NCI, 2007g; 2007i). Factors that play a role in prognosis include age, location and size of tumor, the amount of tumor that can be successfully removed with surgery, and the patient's responsiveness to chemotherapy (Herzog et al., 2005; Lanzkowsky, 2005; NCI, 2007g).

Soft tissue and other extraosseous sarcomas originate in the muscles, tendons, joint tissues, fat, blood vessels, lymph vessels and nerves. These tumors most often originate in the arms, legs, chest, or abdomen (NCI, 2007f). The most common subtype of soft tissue sarcomas affecting children less than 15 years of age are rhabdomyosarcomas (RMS; Lanzkowsky, 2005). Symptom patterns vary with the site of origin (Pappo & Pring, 2000a) although the most common symptom is a mass at the tumor site (Lanzkowsky, 2005). Tumors symptoms can involve the nasal passages (e.g., nosebleeds and congestion), facial palsies, or deformation of the extremities (Roll, 2004). Rhabdomyosarcomas are more prevalent in males and are most often diagnosed between

the ages of 2 and 6 years (Lanzkowsky, 2005; Raney et al., 2005; Roll, 2004). African Americans and females experience lower rates of RMS (Lanzkowsky, 2005). Certain inherited diseases have been identified as risk factors (NCS, 2007f), including Li-Fraumeni syndrome and neurofibromatosis type 1 (Pappo & Pring, 2000a). Other risk factors include acquired immune deficiency syndrome [AIDS], Epstein-Barr virus infection, bilateral retinoblastoma, exposure to radiation therapy (Pappo & Pring, 2000a), anomalies in the central nervous system, genitourinary system, or cardiovascular system, and parental use of marijuana and cocaine (Lanzkowsky, 2005).

Soft tissue sarcomas are staged via two different methods. One method of staging is use of the TNM system. The other method of staging involves assessing the amount of tumor that cannot be surgically-removed (NCI, 2007f). Soft tissue sarcomas have a tendency to reach distal areas of the body via the lymphatic (Raney et al., 2005) or circulatory system (Lanzkowsky, 2005), but the degree of metastasis varies by specific tumor type. Soft tissue sarcomas also tend to spread locally and have high rates of reoccurrence (Lanzkowsky, 2005). The 5-year survival rate for all types of soft tissue sarcoma diagnosed from 1985 through 1994 was 71%. For those children having been diagnosed with RMS between 1985 and 1989, the 5-year survival rate was 60% (Gatta et al., 2002). Males and Caucasian children with soft tissue sarcomas have slightly higher survival rates than do females and African American children (Gurney, Young, Roffers, Smith, & Bunin, 1999). Those children who are younger in age, and who have smaller localized tumors that respond well to therapy have a better prognosis (Lanzkowsky, 2005).

Germ cell tumors, trophoblastic tumors, and neoplasms of the gonads occur when cells from the reproductive organs (either male or female) become malignant. These cells can also metastasize to other areas of the body. Signs and symptoms vary by tumor site (extragonadal, ovarian, or testicular) as does the staging of the disease. These tumors have the capacity to spread to the lungs, liver, lymph nodes, CNS, bones and bone marrow (Lanzkowsky, 2005). These cancers are rare in children less than 15 years of age (NCI, 2007d); incidence rates for this age group approximate 5.4 per 1 million children in the United States (Bernstein, Smith, Liu, Deapen, & Friedman, 2007). Of those occurring in the less than 15 year age group, nongonadal tumors are more commonly diagnosed than are tumors in the gonads (Bernstein, Smith, Liu, Deapen, & Friedman, 1999). Overall, incidence rates are higher in African American youth and, in those cases in children less than 15 years of age, females have slightly higher incidence rates than males (Lanzkowsky, 2005). For tumors of the gonads, Caucasian males have higher incidence rates than African American males, whereas for females the opposite pattern exists (Bernstein, Smith, et al., 1999). These tumors are staged based on the level of metastasis and the success of surgical removal of the tumor (NCI, 2008c). Five-year survival rates for this type of cancer are high, ranging from 90% to 100% (Gatta et al., 2002).

Rare childhood cancers. The final two categories of childhood cancers represent subtypes that occur very rarely in children. They are (a) other malignant epithelial neoplasms and malignant melanomas and (b) other and unspecified neoplasms. Cancers in the former category are more often diagnosed in adolescence and just over 1,000 cases are diagnosed each year in children less than 20 years of age in the United States. The

overall incidence rates for these types of cancer are higher in females than males. Survival rates are approximately 90% and higher for all subtypes. Unlike most other childhood cancers, the risk factors for cancers in this category are more often environmental rather than biological (e.g., exposure to radiation, exposure to the sun) (Bernstein & Gurney, 1999). The latter category of “other and unspecified neoplasms” is used to represent (a) any tumors not better categorized in the other 11 cancer categories, (b) unspecified tumors originating in the digestive, respiratory, and genitourinary systems or the skin (excluding the those of the liver, gonads, or kidneys), (c) tumors that originate at “ill defined and unknown primary sites,” and (d) any potentially misclassified tumors (Steliarova-Foucher et al., 2005). Specific types of rare childhood cancers include: nasopharyngeal carcinoma, other head and neck tumors, salivary gland tumors, laryngeal carcinoma, thyroid tumors, bronchogenic carcinoma, bronchial adenomas, pleuropulmonary blastoma, adrenocortical carcinoma, renal-cell carcinoma, colorectal carcinoma, breast cancer, desmoplastic small round-cell tumor, and skin cancer (melanoma; Pratt, 2000c).

Acute Lymphoblastic Leukemia

Treatment

The most common treatment agents are delivered in the form of chemotherapy, which can be administered orally, intramuscularly, intrathecally (drugs are administered into the cerebral spinal fluid where they will be carried throughout the body), or intravenously (Zins et al., 1998). Intrathecal administration is aimed at preventing leukemic cells from spreading into the CNS (NCI, 2007b). In addition to destroying

malignant cells, these treatment methods also inadvertently damage healthy tissue and cells along the way. Side effects include physical symptoms including hair loss, nausea and vomiting, fatigue, and low resistance to infection (Zins et al., 1998).

The standard treatment protocol for youth with acute lymphoblastic leukemia is broken down into three stages: (a) remission induction, (b) consolidation, and (c) maintenance therapy (NCI, 2007b). Remission induction is designed to kill leukemic cell and put the individual's cancer into a state of remission, or temporary recovery. The consolidation and maintenance therapy stages are designed to eradicate any remaining inactive leukemia cells in the body, in effect preventing a relapse of the cancer (NCI 2007b). The most common treatment for ALL involves the combined use of intrathecal methotrexate (IT MTX) and systemic chemotherapy, which often again incorporates methotrexate—administered intravenously (Margolin, Steuber, & Poplack, 2002). Although methotrexate is a very common drug used to treatment childhood cancer, the optimal dosage level when administering it intravenously has yet to be established (Moe & Holen, 2000).

In current treatment protocols, radiation therapy is generally utilized only for patients with ALL who suffer a CNS relapse because it is widely supported that radiation therapy has a detrimental impact on cognitive and academic functioning (Mulhern, Phipps, & White, 2004). In more high risk cases of ALL, bone marrow transplantation may also be required (Zins et al., 1998).

Social-Emotional, Cognitive, and Academic Impact of ALL and its Treatment

The dramatically increased survival rates of children and adolescents with cancer have initiated the study of cancer and its treatment from a psychological perspective, beginning around the time of the early 1970s. Psychologists have been interested in studying the impact of all cancers and their treatment on numerous areas of functioning, including, cognitive, psychological, and social functioning, educational outcomes and school re-entry issues, quality of life of the patients and their families, and rehabilitation. ALL has received much of this attention because it is the most prevalent of the pediatric cancers. Findings, in general, have remained inconsistent due to methodological variables (e.g., small sample size, heterogeneity of participant groups, variations in time since diagnosis, etc) (Kadan-Lottick & Neglia, 2005; Leigh, 2000; Rourke & Kazak, 2005; Wiard & Jogal, 2000). Furthermore, those children treated with CNS radiation therapy were the main focus of many of these early investigations, as this type of treatment was believed to have worse outcomes (Kadan-Lottick & Neglia, 2005). More recently, however, it has been recognized that children treated with chemotherapy may also be at risk for late-effects, possibly less severe (Leigh, 2000; Kadan-Lottick & Neglia, 2005), but again evidence remains inconclusive (Cruce & Stinnett, 2006) as the many variations in chemotherapy regimens have not all been studied in isolation, and with the methodological rigor necessary to draw firm conclusions. Thus, there remains support for further research to determine if children and adolescents with ALL are equally susceptible to secondary psychological and academic difficulties, to characterize the specific nature of these difficulties, and to describe the psychological, social, and educational functioning of pediatric cancer survivors (Cruce & Stinnett, 2006).

Behavioral functioning. One criticism of studies investigating social-emotional/behavioral functioning in survivors of pediatric ALL is that standardized measures used in these investigations are not specific to their cancer symptomatology (Eiser, Hill, & Vance, 2000). In this regard, a number of studies have been published in recent years that explore the impact of ALL and its treatment on social-emotional/behavioral functioning using measurements other than standardized behavior rating scales. Specifically, Earle and Eiser (2007) conducted semi-structured interviews with the mothers of children having been diagnosed with ALL. Interviews were conducted shortly after diagnosis, and again 1 and 2 years later. Conclusions drawn from mothers' reports indicated that the youngest age group (children 0 to 4 years of age) were initially coping well at diagnosis, evidenced more behavior problems at 1 year post-diagnosis, and then seemed to return to normal behavior at 2 years post-diagnosis. For the middle age group (children 5 to 9 years of age), mothers reported behavioral difficulties from the time of diagnosis, which were maintained or worsened over time to 2 years post-diagnosis. The oldest age group (children and adolescents 10 to 14 years of age) was reported as having the most problem behaviors at diagnosis. They were reported to experience social difficulties including relationship problems, academic difficulties, loneliness and isolation. These social difficulties persisted over time, in addition to growing concerns with appearance, being different from their peers, and trouble cooperating with medical regimens through the 2 years post-diagnosis follow-up.

Eiser and Eiser (2007) used parent rating scales to evaluate mood and behavior in youths treated for ALL. Participants in their sample ranged from approximately 2 to 16

years of age. Parent ratings of their child's or adolescent's mood and behavior problems, measured on a Likert scale, were collected initially between 3 and 5 months post-diagnosis. Subsequent follow-up data were collected at 1 and 2 years post-diagnosis. Participants' mothers were asked to rate their child's or adolescent's current mood and behavior, to retrospectively rate mood and behavior over the previous year, and to make predictions about mood and behavior over the upcoming year. Results indicated that participants' current mood and behavior was rated more positively and these differences were significant between the initial assessment and ratings collected 1 year later. Additionally, ratings of the participant's mood and behavior were significantly correlated (at each time point) with a measure of quality of life. Retrospective ratings of mood and behavior indicated that mothers perceived their child's or adolescent's mood and behavior to be worse at initial assessment than it was prior to diagnosis, but then improving with each subsequent year after diagnosis.

The results from studies such as these can be difficult to interpret, however, because information was not obtained from norm-referenced rating scales and no control/comparison groups were included. Limitations such as these may disguise clinically- and statistically-relevant differences in behavioral functioning between youth with and without ALL. To avoid methodological limitations such as these, other research teams have chosen to measure social-emotional/behavioral functioning using standardized, norm-referenced measurement tools. In this regard, Shelby et al. (1998) demonstrated that youth treated for ALL were statistically different in their behavioral functioning as compared to rating scale norms. They explored functioning in children and

adolescents having successfully completed treatment for ALL. The sample consisted of 32 individuals between the ages of 6 to 17 years. All participants were a minimum of 2 years post-treatment. All participants had been treated with chemotherapy and 20 had additionally received cranial irradiation. Parents completed the Child Behavior Checklist (CBCL; Achenbach, 1991) and the BASC (Reynolds & Kamphaus, 1993).

The results of this investigation indicated that pediatric survivors of ALL had significantly more problems with social competence, adaptive skills, and internalizing problems (i.e., somatic complaints, anxiety, and depression) on both rating scales than would be expected in a normal population. On the CBCL, participants were also rated as having significantly more externalizing behavior problems (i.e., aggression). These behavioral difficulties did not differ significantly as a function of the type of treatment received, nor did age at diagnosis account for any significant variance in the scores. Participants who were older at the time of evaluation were rated as having significantly more problems in the area of adaptive skills than were younger participants. Similarly, Noll et al. (1997) examined the behavioral functioning of survivors of pediatric ALL from parent and teacher perspectives. Their sample consisted of 126 children who were an average of 8 ½ years of age. All participants were in remission at the time of the study and had received treatment through randomized assignment to one of several treatment arms differing based on the use of chemotherapy and cranial irradiation. Parents of these children completed the CBCL—Parent Report Form (CBCL-PRF; Achenbach & Edelbrock, 1983) and the Personality Inventory for Children (PIC; Wirt, Lachar, Klindinst, & Seat, 1984). Teachers were also asked to complete the CBCL—Teacher

Report Form (CBCL-TRF; Achenbach & Edelbrock, 1986). Parents rated their children as having significantly more behavioral problems than did teachers and significantly more behavioral problems than rating scale norms would predict. However, this investigation also did not demonstrate significant differences in the behavioral functioning of children as a function of treatment type or intensity.

Other studies examining functioning in pediatric patients with ALL from the perspective of their teachers have included that of Raymond-Speden and colleagues (2000) who compared four groups of children on measures of behavioral functioning. Their sample included a group of 20 childhood cancer survivors (18 ALL, 2 non-Hodgkin's Lymphoma) who were treated with cranial irradiation and CNS chemotherapy (intrathecal methotrexate), a group of 20 children who survived ALL and had received only CNS chemotherapy (intrathecal methotrexate), 21 children with chronic asthma, and 21 healthy children. All children with cancer had been in remission for at least 20 months. The measures used included the CBCL-PRF and CBCL-TRF (Achenbach & Edelbrock, 1983;1986). While no significant group differences emerged between the two cancer treatment groups, significant differences were noted when children with cancer were compared to the group of healthy children and those having asthma. The combination treatment cancer group was impaired compared to both the healthy comparison group and the asthma group in the areas of academic progress, learning ease, and school competence. The group of participants who had received only chemotherapy also demonstrated areas of impaired functioning when compared with the group of healthy children in the areas of academic progress, learning ease, and school competence.

When compared with the asthma group, children in the group that received only chemotherapy performed significantly worse in the areas of academic progress and learning ease.

Finally, other studies have examined behavioral and social-emotional functioning from the perspective of the pediatric patient with cancer. In general, areas of clinical concern drawn from studies using parent rating scales have not always been evident in studies using self-report measures. For example, Kazak et al. (1997) found that children having survived leukemia (either ALL or AML) did not significantly differ from a group of healthy comparison children with respect to self-reported post-traumatic stress symptoms. The children in the leukemia group were rating such symptoms related to the diagnosis and treatment of their illness, whereas those in the healthy group were reporting on a significant life stressor. There were also no significant relationships found between present age, age at diagnosis, and post-traumatic stress symptoms. Grootenhuis and Last (2001) investigated social-emotional functioning in children and adolescents with cancer that differed in their survival perspectives (one group was in remission, one group had suffered a relapse of their cancer). Participants were between the ages of 8 and 18 years old and had a diagnosis of leukemia, lymphoma, or solid tumor. All were assessed using the Depression Questionnaire for Children (De Wit, 1987), the Trait Anxiety Inventory (Bakker, van Wieringen, van der Ploeg, & Spielberger, 1989), the Defense Scale for Children (Van Veldhuizen & Last, 1991), and the Cognitive Control Strategy Scale for Children (Grootenhuis, Last, De Graaf-Nijkerk, & Van Der Wel, 1996). Gender, age, time since diagnosis, and diagnostic group membership did not significantly predict

depressive or anxiety symptomatology. Thus, the authors concluded that symptoms of anxiety and depression in children with various cancer diagnoses are stable over time and comparable across diagnostic groups. It was noted that participants who were older at the time of evaluation reported significantly less depressive symptoms than those who were younger at the time of evaluation. This latter result is interesting in light of the findings of Portteus, Ahmad, Tobey, and Leavey (2006) who reported that out of 224 pediatric cancer patients' medical records examined, those who were most likely to begin use of anti-depressant medication within 1 year of diagnosis were those patients with ALL, those who were at least 12 years of age, and those who were treated with radiation therapy.

Impairments in behavioral functioning have been noted in youth with ALL. Younger age at diagnosis may serve as a protective factor against long-term behavioral difficulties. Overall, children and adolescents with ALL may also show improvements over time in behavioral functioning. Parent reports of behavioral functioning indicate significant concerns in internalizing and externalizing domains. Teacher reports of behavioral functioning may not be as severe. Finally, youth self-report may not indicate significant levels of behavioral problems.

Quality of life. Reinfjell, Lofstad, Veenstra, Vikan, and Diseth (2007) evaluated quality of life in 40 survivors of ALL. Their sample included participants from 8 ½ to 14 ½ years of age who were between 4 and 12 years post-diagnosis. All participants had been treated with chemotherapy, and one child additionally received radiation therapy. A group of 42 healthy participants was also included as a comparison group. Quality of life

was assessed via participant self-report and parent-report using the Pediatric Quality of Life Inventory (PEDsQL; Varni, Burwinkle, & Seid, 1999). Reinfjell et al. found that compared with healthy peers, survivors of ALL had significantly worse overall quality of life and worse psychosocial health ratings as measured by self-report and parent-report measures. Participants with ALL were also rated (by their parents) as having significantly worse emotional functioning as compared to healthy individuals. Eiser and Eiser (2007) also evaluated quality of life in 46 children and adolescents (between 2 and 16 years of age) being treated for ALL. Parent ratings of quality of life, also measured using the PedsQL, were collected initially between 3 and 5 months post-diagnosis and again at 1 and 2 years post-diagnosis. Parents reported significant improvements in their child's or adolescent's quality of life between the initial assessment and 1 year later. Ratings of quality of life also improved significantly between the second and third assessment periods.

Eiser, Greco, Vance, Horne, and Glaser (2004) compared quality of life in adolescents with ALL and those with CNS tumors, using the PedsQL (Varni et al., 1999) and a semi-structured interview conducted with each participant. The sample consisted of 77 individuals (49 with ALL) who were an average of 14 years of age at the time of evaluation and a minimum of 2 years in remission. Interview data were coded based on discrepancies between what the participant "could do" and "would like to do." Additionally, answers were coded for problem-focused and emotionally-focused coping strategies that were identified from interview answers. Results from the PedsQL indicated that participants with a CNS tumor had significantly poorer physical health, psychosocial

health, and total quality of life scores as compared to rating scale norms. Those individuals with ALL did not differ significantly from rating scale norms. No significant age or gender effects were noted. When the two diagnostic groups were compared on PedsQL subscales, participants in the ALL group reported significantly better physical, social, and school functioning than those in the CNS tumor group. With regard to interview information, participants in the CNS tumor group reported significantly more discrepancies than those in the ALL group in the areas of physical functioning and illness and symptoms. Additionally, during the interview, participants who were older at evaluation, and older at the time of diagnosis reported more discrepancies between what they “could do” and what they “would like to do.”

Children and adolescents with ALL may show impaired quality of life even years after achieving disease remission, although studies have shown that these impairments may show improvement as time from diagnosis increases (e.g., Eiser & Eiser, 2007). These areas of impairment may be less significant than those noted in youth with other types of pediatric cancer (e.g., CNS tumor).

Family functioning. While Kazak et al. (1997) reported that families of the youths surviving ALL or AML were comparable to families of healthy children and adolescents in the areas of family functioning and social support, a number of other investigations have documented impairments in family functioning in those affected by ALL. In this regard, Morris et al. (1997) gathered information from 33 families of children with ALL using the CBCL-PRF (Achenbach & Edelbrock, 1991) and the Family Environment Scale (FES; Moos & Moos, 1986). The scores from these measures were compared with

those of 32 families with healthy children. Child participants were an average of 6 years of age at the time of participation and those with ALL were being treated with both systemic and intrathecal chemotherapy. The families of those children with ALL indicated significantly more problems than did those families with healthy children. Specifically, families of children with ALL reported troubled relationships, characterized by more conflict between and less cohesion among family members. Overall, a main effect for age was noted on measures of externalizing behaviors, with older children displaying more of these behaviors. Significant correlations were also found between measures of family functioning and the child's behavioral functioning as rated on the CBCL-PRF (Achenbach & Edelbrock, 1983). Less cohesive relationships, less sharing/open expression among family members, and families characterized as more controlling were correlated with a child's internalizing behaviors on the CBCL-PRF. Conversely, externalizing behaviors on the CBCL-PRF were correlated with families rated as higher in conflict and lower in levels of allowed child independence. However, despite evidence for disrupted family relationships in those families affected by ALL, many of the same families did not rate their children as having clinically significant behavioral difficulties on the CBCL-PRF.

Disruptions in family functioning in those families of youth with ALL may be particularly noticeable in families of those children and adolescents during treatment. For example, families interviewed around the time their child entered remission reported difficulties in trying to maintain normality in their everyday lives. This change was partly

attributed to developmental regressions experienced by the child undergoing treatment, and subsequent changes to the parent-child relationship (McGrath, 2001).

The negative effects of ALL on family functioning have also been observed in the adolescent age group. Manne and Miller (1998) examined social conflict and levels of adjustment in a pediatric cancer population. Their sample was composed of participants 12 to 20 years of age with a variety of pediatric cancer diagnoses including ALL, as well as a group of healthy adolescents. The authors found that families of adolescents with cancer had significantly higher levels of parent-adolescent conflict, and higher levels of emotional distress related to perceived maternal antagonism/conflict. The authors concluded that a possible reason for higher levels of conflict in the cancer group was due to the illness and its treatment interfering with the adolescent's normal progression toward independence.

The quantity and quality of social support, as perceived by those children and adolescents having ALL, has also been investigated. For example, Greszta (2006) utilized narrative techniques to evaluate the perceptions of social support in a group of childhood ALL survivors treated with chemotherapy, and compared these with a group of demographically-matched healthy children. The sample was comprised of 67 children who were approximately 7 years of age at the time of diagnosis. Results indicated that both groups perceived parental figures as their primary source of social support. The results indicated that while children with ALL perceived significantly more social support than did their non-chronically-ill peers, they felt the quality of this social support was significantly less intense than the support reported by the healthy group. Manne and

Miller (1998) also examined perceived levels of social support but did not find significant differences between youth with cancer and non-chronically-ill youth. These results are difficult to interpret with respect to individuals with ALL because the cancer group was heterogeneous with respect to diagnosis.

In conclusion, families dealing with the diagnosis and treatment of childhood ALL may be affected by more troubled family relationships, including more conflict and less cohesion among family members. Issues such as these may negatively impact the amount of social support that children and adolescents with ALL perceive from their family members.

Intelligence and achievement. A number of recent studies have examined intelligence and academic achievement in pediatric patients with ALL, but have only measured IQ and achievement scores at a single point in time. For example, MacLean et al. (1995) evaluated intellectual performance in pediatric patients with ALL using the McCarthy Scales of Children's Abilities (MCSA; McCarthy, 1972). Participants included 74 children (between 3 and 6 ½ years of age) with ALL, who were randomized to received either cranial irradiation in addition to intrathecal methotrexate, or intrathecal methotrexate alone. Intellectual data were collected between 8 and 10 months post-diagnosis and no significant group differences were observed. Reinfjell et al. (2007) evaluated intellectual performance in a sample of 40 survivors of ALL and 42 healthy comparison peers who ranged from 8 ½ to 14 ½ years of age. Participants with ALL were between 4 and 12 years post-diagnosis and had been treated with chemotherapy. One participant had additionally received radiation therapy. Intellectual performance was

measured using the Wechsler Intelligence Scales for Children—Third Edition (WISC-III; Wechsler, 1991). Although group means on the Full Scale IQ, Verbal IQ, and Performance IQ scores were each within the average range, statistically significant differences were observed, with participants in the ALL group having lower scores in each area. Brown et al. (1998) also found that children treated for ALL performed within the average range overall on measures of intelligence and academic achievement. They evaluated 47 children and adolescents with ALL treated with triple intrathecal therapy (chemotherapy) using the WISC-III (Wechsler, 1991) and the Woodcock-Johnson—Revised, Tests of Achievement (WJ-R; Woodcock & Johnson, 1989). At the time of diagnosis, participants ranged from 1½ years to 15 ½ years of age. All participants were evaluated at least 2 years post-treatment. Results indicated that individuals with ALL performed within the average range on all measures, but within group gender differences were evident on the Performance IQ score, Perceptual Organization Index score, and Freedom from Distractibility Index score. Specifically, females performed worse than males in these areas.

Schatz, Kramer, Ablin, and Matthay (2000) compared 27 survivors of ALL (all of whom received intrathecal methotrexate chemotherapy as treatment, and 18 of those children additionally received cranial irradiation) to 27 healthy comparison peers who were age and gender matched to the ALL group. The average age at diagnosis for the ALL groups was 6 years. With regard to time in remission, the combination treatment group was an average of 12 years from achieving remission, whereas the chemotherapy-only group was an average of 7 years from achieving remission. All participants were

assessed using the Kaufman Brief Intelligence Test (K-BIT; Kaufman, 1985), the Reading and Arithmetic subtests from the Wide Range Achievement Test—Third Edition (WRAT-3; Wilkinson, 1993). Significant differences were only evident between the group that had received radiation therapy and the healthy comparison group, with the radiated ALL group performing worse on measures of intelligence, reading, and arithmetic.

Raymond-Speden et al. (2000) compared four groups of children on measures of intellectual and academic functioning. Their sample included a group of 20 childhood cancer survivors (18 ALL, 2 non-Hodgkin's Lymphoma) who were treated with cranial irradiation and intrathecal methotrexate, a group of 20 children who survived ALL and had been treated with intrathecal methotrexate only, 21 children with chronic asthma, and 21 healthy children. All children with cancer had been in remission for at least 20 months. The measures used included the Wechsler Intelligence Scale for Children, Revised (WISC-R; Wechsler, 1974) or Wechsler Adult Intelligence Scale, Revised (WAIS-R; Wechsler, 1981), and Wide Range Achievement Test (WRAT; Jastak & Jastak, 1978). Significant group differences emerged in the areas of intellectual function and academic performance. Specifically, the combination treatment cancer group performed worse than the group of healthy children on the Full Scale IQ, Verbal IQ, and Performance IQ scores, Verbal Comprehension, Perceptual Organization, Freedom from Distractibility index scores, and the Arithmetic subtest. When compared with the asthma group, the cancer combination treatment group performed significantly worse on measures of Full Scale IQ and Verbal IQ score, and Verbal Comprehension and

perceptual organization index scores. The chemotherapy-only group also performed significantly worse than the group of healthy children in Full Scale IQ, Verbal IQ, and Performance IQ scores, and verbal comprehension index score. When compared with the asthma group, participants in the chemotherapy-only group performed significantly worse in Performance IQ score. When the two cancer treatment groups were compared, no significant group differences emerged.

Anderson, Anderson, and Anderson (2006) also compared intellectual functioning in pediatric patients with ALL to other groups with chronic conditions. Their sample included 184 individuals with one of the following conditions: attention-deficit/hyperactivity disorder, traumatic brain injury, insulin-dependent diabetes mellitus, and ALL (31 of the participants), and a group of healthy participants. The participants with ALL had received intrathecal methotrexate and cranial irradiation as part of their treatment. All participants were evaluated with the WISC-III (Wechsler, 1991) and those in the ALL group were found to have significantly lower Full Scale IQ scores compared to all other groups.

Précourt et al. (2002) evaluated females who were an average of 30 months past completion of treatment for ALL. Ten participants were treated with chemotherapy only, 9 were treated with chemotherapy and cranial irradiation. Ten healthy comparison females were also included. The measures used included the WISC-III (Wechsler, 1991) and the Passage Comprehension and Calculation subtests from the WJ-R (Woodcock & Johnson, 1989). All groups performed within the average range on the measure of intelligence, although those participants who had received radiation therapy obtained a

lower mean Full Scale IQ score than the chemotherapy-only group, which in turn, obtained a lower mean Full Scale IQ than the healthy group. Similar significant group differences were found for the Verbal IQ and Performance IQ scores, and Verbal Comprehension Index, Perceptual Organization Index, and Freedom from Distractibility Index scores. The two subgroups of participants with ALL differed significantly in their scores on the Freedom from Distractibility Index and Arithmetic subtest, with the group treated with radiation performing worse. Those children who had received radiation therapy also performed significantly worse on the Vocabulary, Information, Similarities, Digit Span, and Block Design subtests as compared with the group of healthy peers. No significant group differences were apparent on Calculation. For those participants treated with chemotherapy only, age at diagnosis was significantly related to lower scores on nonverbal tasks and Full Scale IQ and longer time since treatment was significantly associated with poor performance on Digit Span.

Langer et al. (2002) also demonstrated the detrimental impact of radiation therapy for ALL on intellectual and academic functioning. Their sample included 121 participants that had completed treatment for ALL a minimum of 4 ½ years prior to the study. The participants ranged from 4 months of age to 16 years of age at diagnosis. Thirty-eight of the participants received chemotherapy only, whereas the remaining 83 received radiation as part of their treatment for ALL. Results indicated that participants previously treated with radiation therapy scored significantly lower than the chemotherapy-only group in Full Scale IQ, Verbal IQ, and Freedom from Distractibility Index scores. All participants younger than 5 years of age at the time of diagnosis performed significantly worse on

measures of Performance IQ and the Perceptual Organization Index. No significant main effects for gender differences were found. However, a significant two-way interaction was noted for males treated with radiation therapy, a subgroup that performed worse in Full Scale IQ, Verbal IQ, Performance IQ, Verbal Comprehension Index, and Perceptual Organization Index scores.

Hill et al. (1997) also measured intellectual performance with the WISC-III (Wechsler, 1991), but arrived at different results—impaired intellectual functioning in pediatric patients with ALL treated with chemotherapy only. Participants in their sample consisted of 10 ALL survivors (aged 1 to 5 years at diagnosis and a minimum of 3 years post-diagnosis at the time of evaluation) and 10 healthy comparison participants. Children with ALL performed in the borderline to low average range of intelligence on all major composite scores of the WISC-III, which was significantly worse than the performance of the healthy comparison group. Similarly, Lofstad, Reinfjell, Hestad, and Diseth (2008) examined cognitive functioning in a group of 35 survivors of pediatric ALL who had been treated only with chemotherapy. A group of 35 healthy participants, age and gender matched to the ALL participants, was also included. Participants with ALL were an average of 11.5 years of age at evaluation, 3.8 years of age at diagnosis, and 7.7 years post-diagnosis. Participants were evaluated using the WISC-III, Swedish version with Norwegian translation (Wechsler, 1991; Wechsler, 2004). The results of this study indicated that participants with ALL performed significantly worse on measure of Full Scale IQ, Verbal IQ, and Performance IQ as compared with healthy control participants, and worse with regard to Verbal IQ performance when compared with test

normative data. Additionally, analyses of performance on subtests and index scores contributing to these composites revealed that the average performance of participants with ALL was significantly worse than healthy controls, and when compared to test normative data, on the Freedom from Distractibility Index and Processing Speed Index scores, and the Arithmetic and Symbol Search subtests. Participants with ALL also performed significantly worse on the Block Design and Object Assembly subtests when compared with healthy control participants, but results were not significant when compared with test normative data.

Reeves et al. (2007) examined *sluggish cognitive tempo* in pediatric survivors of ALL and a group of healthy siblings and the impact of this characteristic on intellectual functioning and academic achievement. The sample included 80 participants with ALL, of which 67 had been treated only with chemotherapy and 13 had been treated with cranial irradiation, with an average age at testing of 12.4 years old. Participants with ALL were an average of 6 years post-treatment completion. The sibling participant group included 19 individuals who were an average of 12.6 years of age. The measures used included the CBCL (Achenbach, 1991)—with specific interest in items that had been shown in previous research (Hartman et al., 2004) as indicative of sluggish cognitive tempo— in addition to the WISC-III (Wechsler, 1991) or WAIS-III (Wechsler, 1997), and the Wechsler Individual Achievement Test (WIAT; The Psychological Corporation, 1992). The results indicated that participants with ALL performed significantly worse on measures of basic reading skills and were significantly worse with regard to symptoms of sluggish cognitive tempo, as measured by the CBCL, than were healthy sibling

participants. Furthermore, symptoms of sluggish cognitive tempo were reported to partially account for the identified between group differences on measures of basic reading skills. No other group differences were significant. Further analyses revealed that symptoms of sluggish cognitive tempo were significantly related to worse performance on measures of intellectual function, basic reading and reading comprehension skills, and math calculation and problem solving skills.

Several studies have used longitudinal design to evaluate the intellectual and academic performance changes that occur in pediatric patients with ALL. For example, Andrews Espy et al. (2001) examined intellectual and academic performance in children and adolescents with ALL who were treated at 2 prominent child cancer centers. Treatment protocols varied between the two sites, with participants receiving only intrathecal methotrexate at one site; participants at the other site received both systemic and intrathecal chemotherapy. The sample was comprised of 30 children and adolescents ranging in age from 1 to 17 years old at diagnosis. The participants were evaluated with the WISC-R (Wechsler, 1974), MCSA (McCarthy, 1972), and WRAT-R (Jastak & Jastak, 1984) at 8 months post-diagnosis, and then again at 2, 3, and 4 years post-diagnosis. The results of this study revealed that statistically significant declines in performance were noted for the entire sample on measures of arithmetic ability. However, group means on all measures remained in the average range at 4 years post-diagnosis.

Brown et al. (1999) evaluated 16 children who had received chemotherapy as CNS prophylaxis (14 with ALL, 1 with AML, and 1 with T-cell lymphoma) and 10

children with other types of cancer (excluding brain tumors) who did not receive CNS prophylaxis as part of their treatment. Significant group differences were noted in performance on the WISC-R Full Scale IQ and Verbal IQ scores at 3 years post-diagnosis and on the Full Scale IQ and Performance IQ at 4 years post-diagnosis. Within group trends revealed that the group of children with leukemia performed worse on IQ composite scores over time, although these differences were not statistically significant. In contrast to this, the full scale and Performance IQ scores of children in the other group increased significantly over time. With respect to academic achievement, significant group differences emerged at 3 years post-diagnosis on measures of reading, spelling, and arithmetic. Only the significant differences on the reading measure persisted to 4 years post-diagnosis.

Montour-Proulx et al. (2005) examined retrospective data on cognitive functioning in 24 children treated for ALL with chemotherapy only. Their sample was an average of 5 years of age at diagnosis. Intellectual performance was assessed using the WPPSI-R (Wechsler, 1989), the WISC-III (Wechsler, 1991) or the French-Canadian adaptation of the WISC-III (Wechsler, 1991). Because the cognitive data was not originally collected for research purposes, the number and timing of evaluations was not standard across participants. From review of records, however, the authors were able to conclude that children with ALL had IQ scores in the low average range overall and that approximately 50% of the subtest scores contributing to Verbal and Performance IQ composite scores exceeded 1 standard deviation below the mean. Over time, children

with ALL seemed to show declines in Performance IQ scores, and their IQ scores overall were significantly different than test means.

Brown et al. (1996) failed to find significant declines in intellectual and academic performance over time for children and adolescents with leukemia. Their sample included participants with leukemia (29 ALL and 9 AML) who were treated only with chemotherapy and 25 individuals with other cancers (excluding leukemia and brain tumors) not treated with CNS prophylaxis. All participants were between the ages of 2 and 15 years at the time of initial assessment. Evaluations were conducted approximately 5 weeks post-diagnosis, and then yearly thereafter for 3 years. The measures used included the MCSA (McCarthy, 1972), the WISC-R (Wechsler, 1974) or the WAIS-R (Wechsler, 1981), and the Wide Range Achievement Test-Revised (WRAT-R; Jastak & Jastak, 1984). No significant differences were found between groups on measures of intellectual performance or academic achievement. However, children with leukemia did demonstrate clinically significant declines (change in scores that equaled or exceeded 1 standard deviation) in performance on measures of reading, spelling, and arithmetic over the 4-year period.

Kaemingk, Carey, Moore, Herzer, and Hutter (2004) reported on mathematics performance in survivors of pediatric ALL as compared to healthy participants. None of the participants with ALL had been treated with cranial irradiation. Instead they received systemic and triple intrathecal chemotherapy only. The sample was composed of 15 individuals per group who were an average of 12 years of age, and those with ALL were an average of 5 years post-treatment. The measures used included the Arithmetic subtest

from the WISC-III (Wechsler, 1991)/WAIS-III (Wechsler, 1997), the Calculation and Letter-Word Identification subtests from the WJ-R (Woodcock & Johnson, 1989), the KeyMath, Revised (KeyMath-R; Connolly, 1988), the Controlled Oral Word Association Test (COWA; Benton & des Hamsher, 1989), the Visual-Motor Integration Test (VMI; Beery, 1997), the Purdue Pegboard Test (PPT; Tiffin, 1968), and the Story and Design Memory tests from the Wide Range Assessment of Memory and Learning (WRAML; Sheslow & Adams, 1990). Kaemingk et al. found significant group differences when comparing participants with ALL to healthy peers. Specifically, the ALL group performed significantly worse on the following measures: Arithmetic, KeyMath-R Total score, Basic Concepts score, and Applications score. Their performance on KeyMath-R Operations score was also significantly below the test mean score. On other measures used, the ALL group performed significantly worse than their healthy peers on the VMI, and worse than normative expectation on the Purdue Pegboard Test (with both dominant and non-dominant hands). Correlation analyses revealed that performance on math measures was most related to performance on verbal and visual memory measures, and dominant hand speed.

In summary, recent investigations of intellectual and academic performance in children treated for ALL have revealed several interesting findings. Measures of intellectual and academic performance at a single time point may yield statistically significant group differences (e.g. comparing youth with ALL to healthy peers) but scores may not be clinically meaningful as they remain in the average range overall. When different types of treatment for ALL have been compared, pediatric patients treated with

radiation appear to fare worse than do those treated only with chemotherapy, although not all studies support this conclusion. Several methodological limitations contribute to the inconsistency in these findings including mixed diagnostic and/or mixed treatment groups and small sample sizes.

Neuropsychological function. A variety of studies have examined various domains of neuropsychological function in children with ALL. However, Boman (2007) asserted that a continued need for exploration exists in this area that employs large sample sizes, standardized assessment measures, and longitudinal design.

Attention. Anderson et al. (2006) compared attention skills in 184 children with one of the following conditions: attention-deficit/hyperactivity disorder, traumatic brain injury, insulin-dependent diabetes mellitus, and ALL (31 of the participants), as well as a group of healthy comparison children. The children with ALL were treated with intrathecal methotrexate and cranial radiation therapy. Continuous performance tasks (CPT) designed to measure selective and sustained attention, response inhibition/impulsivity, and processing speed were used. Results indicated that mean performance of the ALL group was not significantly different from that of the group of healthy children.

Lamothe, Robaey, Précourt, Kabéné, and Moghrabi (1998) evaluated visual attention in 10 female survivors of ALL who had been treated with intrathecal chemotherapy only, 9 treated with intrathecal chemotherapy in addition to cranial radiation therapy, and 10 females not having leukemia. All were in between the ages of 6 and 11 years at the time of evaluation and all survivors of leukemia were a minimum of

18 months post-treatment. All participants were of normal intelligence although the participants with ALL had significantly lower Full Scale IQ than the group of healthy participants. The task designed to measure visual attention required participants to quickly and accurately identify two different visual stimuli, one of which appeared more frequently (“frequent”) than the other (“rare”). No significant group differences emerged for accuracy or response time, although the ALL group had longer response latency to both frequent and rare stimuli overall. The group of children with leukemia who were treated only with intrathecal chemotherapy had a significantly smaller difference between their response latency to frequent versus rare visual stimuli than did the other two groups.

In another study, Lockwood, Bell, and Colegrove (1999) evaluated attention in 56 survivors of ALL who were randomly assigned to receive either radiation in addition to intrathecal chemotherapy or chemotherapy alone. The participants ranged from approximately 1 to 18 years of age at diagnosis and were a minimum of 6 years in remission. There were 28 individuals in each treatment group. The measures used included the WAIS-R (Wechsler, 1981) or WISC-III (Wechsler, 1991), the California Verbal Learning Test (CVLT or CVLT-C; Delis, Kramer, Kaplan, & Ober, 1987, 1994), the COWA (Benton & des Hamsher, 1989), the Rey-Osterrieth Complex Figure Test (Rey, 1941), the Stroop Color and Word Test (Golden, 1978), the Test of Variables of Attention (Greenberg & Dupuy, 1993), and the Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). Performance on these measures was grouped in various ways to form four components of attention: sensory selection, response selection, attentional capacity, and sustained attention. Results indicated that the treatment groups

differed significantly in the areas of sensory selection, attentional capacity, and sustained attention, with the group receiving radiation therapy performing worse. Furthermore, the children treated with radiation prior to the age of 4 ½ years old performed significantly worse on sensory selection. These young children treated with radiation therapy were also significantly impaired on sensory selection, response selection, sustained attention, and attentional capacity as compared with participants treated only with chemotherapy prior to the age of 4 ½ years. Overall, the authors concluded that survivors of ALL who were treated with radiation therapy at a young age suffered impairments in their ability to focus attention, shift attention, ability to manage large amounts of material, formulate hypotheses, and sustain attentional readiness for long periods of time. Those survivors who treated with radiation therapy after 4 ½ years of age also suffered attention impairments but they were milder in nature and confined to the functions of mental switching and sustained attention only. In contrast, survivors who received only chemotherapy as treatment for ALL performed within normal limits on measures of attention.

Schatz, Kramer, Ablin, and Matthay (2004) examined visual attention in survivors of ALL who were treated with cranial irradiation. They compared 21 survivors of ALL who were at least 9 years of age at the time of evaluation and a minimum of 30 months in remission, and a group of 24 healthy peers. Within the ALL group, 13 participants received radiation therapy in addition to intrathecal chemotherapy, while the remainder received intrathecal chemotherapy only. All participants were assessed in the areas of visual attention orienting and global versus local attention (a hierarchical attention task).

The findings from this study indicated that survivors of ALL treated only with chemotherapy performed similarly to healthy peers on measures of visual attention, whereas those treated with radiation therapy had significant difficulties with shifting attention both spatially and hierarchically as compared to healthy peers. Young age at the time of treatment with radiation accounted for the group differences.

Memory. Montour-Proulx et al. (2005) examined an existing database of the memory and learning performance in 24 individuals treated for pediatric ALL with chemotherapy only (no radiation therapy). The participants were an average of 5 years old at diagnosis and had been evaluated at various points in time. Memory and learning were assessed using the WRAML (Sheslow & Adams, 1990). When compared with test norms, the participants' memory scores differed significantly over time. For verbal memory measures, 50% of participants' scores exceeded 1 standard deviation below the test mean; on visual memory measures 35% of scores exceeded 1 standard deviation below the test mean. Hill et al. (1997) also used the WRAML (Sheslow & Adams, 1990) to measure memory performance in children treated for ALL. Their sample consisted of 10 ALL survivors (aged 1 to 5 years at diagnosis and a minimum of 3 years post-diagnosis at the time of study) who had been treated with intrathecal chemotherapy but not radiation therapy, and 10 healthy children. Survivors of ALL performed significantly worse than children in the healthy comparison group, and when compared to test norms, on measures of short-term verbal memory and short-term visual memory. Children in the ALL group continued to perform significantly worse than test norms and their healthy counterparts on measures of visual memory even after repeated exposures to information.

Performance on these memory measures was also found to be positively correlated with intelligence, with children in the ALL group having higher correlations between their scores.

Kleinman and Waber (1994) examined the immediate recall performance of 34 survivors of ALL on a prose memory subtest from the Wechsler Memory Scale—Revised (WMS-R; Wechsler, 1987) and compared them to a group of 33 age- and gender-matched healthy individuals. The age range of the sample was 10 to 16 years of age. Participants in the ALL group were 60 to 112 months post-diagnosis. Results indicated that survivors of ALL may experience memory problems as compared to healthy individuals.

Participants with leukemia remembered less information, but their organization of story elements was similar to that of healthy peers. Error analysis indicated that story recall errors of healthy participants were more often additions or assumed information, whereas those of the ALL group were more often characterized by ambiguous or missing information. Children in the ALL group made more errors overall. Schatz et al. (2000) compared 27 survivors of pediatric ALL (all of whom had received intrathecal methotrexate chemotherapy as treatment, and 18 of those participants additionally received cranial radiation therapy) to 27 healthy comparison peers who were age and gender matched to the ALL group. Participants were an average of 6 to 7 years of age at diagnosis; average time in remission varied from 7 to 12 years depending on group membership. All participants were assessed using computer-based tasks designed to assess working memory (verbal and visual-spatial) and processing speed. The group treated with radiation therapy performed significantly worse on measures of working

memory as compared to healthy counterparts, with worse performance on the spatial memory tasks. In contrast, the chemotherapy-only group's performance was comparable to that of the healthy group.

Carey et al. (2006) also reported on the performance of children with ALL, treated with chemotherapy alone, across measures of Full Scale IQ (WASI; Wechsler, 1999), working memory (SB-IV Memory for Sentences and Bead Memory subtests; Thorndike et al., 1986a), nonverbal skills (VMI; Beery 1997; WASI Block Design subtest; Wechsler, 1999), and verbal skills (PPVT-III; Dunn & Dunn, 1997; WASI Vocabulary subtest; Wechsler, 1999) collected shortly after diagnosis and again one year later. Carey et al. found that during the first year of treatment for ALL, working memory scores were significantly impacted. On measures of working memory, a significant group x time interaction was noted; participants in a group receiving a lower dosage of intravenous chemotherapy showed increases in performance, while participants from a group receiving higher dosages of intravenous chemotherapy showed declines in performance. Despite these differences however, group means remained within the average range of performance on all measures at both time points.

Perceptual-motor. Several studies have examined perceptual-motor functioning and found that both chemotherapy and radiation therapy may have a detrimental impact on these areas of functioning in children and adolescents with ALL. Ciesielski et al. (1994) reported that children treated for ALL with cranial radiation and intrathecal chemotherapy suffer deficits in visual-spatial-motor coordination and memory and are prone to impairments in the area of sensory-motor learning, which are evident years after

the cessation of treatment. Raymond-Speden et al. (2000) compared four groups of children on measures of neuropsychological functioning. Their sample included a group of 20 childhood cancer survivors (18 ALL, 2 non-Hodgkin's Lymphoma) who were treated with cranial radiation and CNS chemotherapy (intrathecal methotrexate), a group of 20 children who survived ALL and had been treated with CNS chemotherapy (intrathecal methotrexate) only, 21 children with chronic asthma, and 21 healthy children. All children with cancer had been in remission for at least 20 months. Measures used included the Trail Making Test for Children (TMT-C; Reitan, 1969) and the Benton Visual Retention Test (Benton, 1974). The chemotherapy-only group performed worse on the Trail Making Test when compared to children with asthma and healthy children. Interestingly, comparison between the two cancer treatment groups yielded no significant findings.

Andrews Espy et al. (2001) examined visual-motor integration with the VMI (Beery, 1997) in children with ALL treated at two prominent child cancer centers (see page 62 for description of methodology). Findings from the analysis of performance on visual-motor skill indicated that children treated for ALL (regardless of treatment type) showed declines in performance on the VMI, however the differences were not large enough to be statistically significant. When examining differences between the two treatment groups, children receiving combination chemotherapy experienced larger (and statistically significant) decrements in performance in the area of visual motor integration over time. Despite declines in performance, group means on all measures remained in the average range at 4 years post-diagnosis. Brown et al. (1998) evaluated 47 children and

adolescents with ALL treated with triple intrathecal therapy. At the time of diagnosis, participants ranged in age from 1 ½ years to 15 ½ years old. All participants were a minimum of 2 years post-treatment at the time the study was conducted. Participants with ALL were found to perform in the average range on the VMI (Beery, 1997), although their scores were still significantly below the test mean. When gender was factored in, these significant differences were attributable to females only. Van Brussel et al. (2006) reported that survivors of pediatric ALL, treated with chemotherapy only (no cranial irradiation) may evidence visuomotor control impairments even as late as 5 to 6 years post-treatment completion.

Mahone, Prahme, Ruble, Mostofsky, and Schwartz (2007) evaluated 22 children and adolescents treated for ALL with intrathecal chemotherapy but no cranial radiation therapy. Participants in their sample ranged in age from 8 to 18 years, and were between 3 and 11 years post-treatment completion. Twenty-two demographically-matched healthy individuals also participated. All participants completed tasks designed to measure motor speed, and auditory perception of timing and pitch. Their findings indicated that participants treated for ALL showed decrements in performance on measures of motor and perceptual timing as compared with healthy peers.

Carey et al. (2006) also reported that performance on measures of nonverbal skills (VMI; Beery 1997; WASI Block Design subtest; Wechsler, 1999), collected shortly after diagnosis and again 1 year later, a significant main effect for group was observed. Specifically, participants receiving a lower, extended dose of intravenous methotrexate (Group 1) outperformed those participants who were treated with a higher, shorter dose

of intravenous methotrexate (Group 2) at both assessments on nonverbal measures.

Despite these differences however, group means remained within the average range of performance on all measures at both time points.

Buizer et al. (2005) also evaluated the impact of pediatric ALL and treatment with chemotherapy on visuomotor control. Participants included 34 survivors of ALL, between the ages of 4 ½ and 18 years old at the time of evaluation, who were in complete remission and at least 1 year post-treatment completion. Additionally, 38 participants (age and gender matched) who were at least 1 year post-treatment completion for Wilm's tumor were included. Siblings of participants in each group served as a comparison group along with another 108 age-matched healthy peers. The ALL group had received chemotherapy as treatment in the form of intrathecal (either via triple intrathecal therapy or methotrexate alone) and systemic chemotherapy. All participants were evaluated using measures of visual reaction time, visual tracking, and visual pursuit. No group or gender differences were found on measures of visual reaction time, tracking accuracy or stability. The ALL group performed significantly worse than controls on the measure of visual pursuit accuracy and stability. The group differences in visual pursuit stability were most evident in girls (i.e., a significant group x gender interaction emerged). For visual pursuit stability, female gender, shorter time since treatment, and higher chemotherapy dosage levels (for girls only) were risk factors for impaired performance. The authors concluded that survivors of ALL who were treated only with chemotherapy demonstrated impaired performance only on those visuomotor tasks that were the most cognitively demanding.

Language. Children with ALL may be impaired on measures of word association (Jordan, Murdoch, Hudson-Tenet, & Boon, 1996). Précourt, Lamothe, Lassonde, Sauerwein, and Moghrabi (2002) assessed language abilities in female children treated for ALL. Participants included 10 individuals were treated with chemotherapy only, 9 treated with chemotherapy and cranial irradiation, all of which were evaluated an average of 30 months post-treatment completion, and 10 healthy comparison peers. The measures used included the WISC-III (Wechsler, 1991), the CVLT-C (Delis et al., 1987, 1994) and the Passage Comprehension subtest from the WJ-R (Woodcock & Johnson, 1989). Participants treated with radiation therapy performed significantly worse on verbal measures from the WISC-III (vocabulary, information, similarities, and digit span) than did healthy peers. Both ALL groups performed significantly worse than healthy peers on measures of verbal learning and memory from the CVLT-C (specifically immediate recall, cued recall, and long delayed recall), and Passage Comprehension. Similarly, Lofstad et al. (2008) found that participants with ALL, who were treated only with chemotherapy performed significantly worse than a group of healthy control participants on measures of language function (see page 60 for review of methodology). Measures on which significant group differences were revealed included the Verbal Comprehension Index, and Comprehension, Similarities and Vocabulary subtests from the WISC-III (Swedish version; Wechsler, 2004). Additionally, the performance of participants with ALL was also significantly below test normative data (i.e., test means) on the Similarities and Vocabulary subtests.

Stehbens et al. (1994) examined the neuropsychological performance in youths with ALL. Their sample included participants who were between 6 ½ and 19 years of age at initial evaluation. Participants were randomly assigned to one of 2 treatment protocols, with 23 participants receiving cranial radiation therapy and intrathecal methotrexate and 19 participants receiving intrathecal methotrexate only. Initial neuropsychological evaluations were conducted at 9 months post-diagnosis. Several domains of functioning were assessed, but those measures used to evaluate language skills included the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964), the WISC-R (Wechsler, 1974) and WAIS-R (Wechsler, 1981), the Peabody Picture Vocabulary Test--Revised (PPVT-R; Dunn & Dunn, 1981), the Token Test for Children (DiSimoni, 1978), the Rapid Automatized Naming Test (Denckla & Rudel, 1974), the FAS Fluency measure (Spreeen & Benton, 1969), and the Sentence Repetition Test (Carmichael & MacDonald, 1984). Significant group differences were found between those participants treated with radiation therapy and those receiving chemotherapy only. Individuals who received radiation therapy performed significantly worse on Sentence Repetition and delayed recall from the RAVLT, although this group difference could have been predicted by chance alone.

MacLean et al. (1995) measured receptive language performance in children with ALL treated with and without cranial irradiation. Participants included 74 children with ALL between the ages of 3 and 6 ½ years old who were randomized to receive either cranial irradiation in addition to intrathecal methotrexate, or intrathecal methotrexate alone. Receptive language was evaluated using the PPVT-R (Dunn & Dunn, 1981) and

the Token Test for Children (DiSimoni, 1978). Evaluation data were collected between 8 and 10 months post-diagnosis. Results indicated that children who received cranial radiation in addition to chemotherapy performed significantly worse on one measure of receptive vocabulary (Token test). Andrews Espy et al. (2001) also examined language skills in youths with ALL. Participants in their sample ranged from 1 to 17 years of age at diagnosis and had been treated with either intrathecal chemotherapy or a combination of intrathecal and systemic chemotherapy. Evaluations were conducted at approximately 8 months post-diagnosis and then again at 2, 3, and 4 years post-diagnosis using the CVLT-C (Delis et al., 1987, 1994) and the COWA (Benton & des Hamsher, 1989). Findings from this study indicated that individuals treated for ALL (regardless of treatment type) showed statistically significant declines in verbal fluency performance over time. However, despite these declines in performance, group means on both measures remained in the average range at 4 years post-diagnosis.

In summary, pediatric survivors of ALL who were treated with chemotherapy only have not been found to have significant impairments in performance on measures of attentional functioning; in general they perform similarly to healthy peers on these tasks. However, all recent studies examining this domain of functioning have failed to employ a longitudinal design. Declines in performance on both verbal and visual memory tasks have been found in pediatric patients with ALL, regardless of treatment type. However, children and adolescents treated with radiation therapy may show more memory deficiencies than those treated with chemotherapy alone. Visual-motor functioning may also be negatively affected by ALL and its treatment although several studies have shown

that overall visual-motor skills in pediatric patients treated for ALL remains in the average range even if relative declines in scores are noted over time. Language skills appear to be relatively preserved in children and adolescents treated for ALL with chemotherapy only. Those treated with radiation therapy have, in some instances, shown statistically significant differences in language functioning as compared with healthy individuals.

CHAPTER 3

METHOD

Participants

Participants in this study were obtained from a database of pediatric patients diagnosed with ALL who were recruited between 1999 and 2001 to participate in research at the University of Arizona College of Medicine, Section of Pediatric Hematology/Oncology, Department of Pediatrics and from the Texas Children's Cancer Center, Texas Children's Hospital, Baylor College of Medicine. These two institutions collaborated in this research because they have uniform treatment protocols for ALL (consistent with Pediatric Oncology Group [POG] and Children's Oncology Group [COG] protocols), which includes the use of triple intrathecal chemotherapy and intermediate dose intrathecal methotrexate that is based on ALL risk level. At the time of protocol enrollment on POG or COG protocols, participants were randomly assigned to receive one of two different doses of intravenous methotrexate (IVMTX)—either $1\text{g}/\text{m}^2$ over 24 hours or $2\text{g}/\text{m}^2$ over 4 hours—during the consolidation phase of treatment. Each participant received a total of six infusions during this treatment phase. Additionally, all participants received intrathecal methotrexate (ITMTX) as central nervous system prophylaxis according to standardized dose schedules. No participants underwent treatment with radiation therapy. The treatment timeline was as follows: a) remission induction phase lasted from diagnosis through day 28, b) consolidation lasted from week 5 through week 32, and c) maintenance lasted from week 33 through week 130 for each participant.

Participants with ALL were assigned a risk level based on a standardized method of determining risk for disease relapse. This score is assigned by the Central Operations Office of the Children's Oncology Group and is based on three factors: a) white blood cell count at the time of ALL diagnosis, b) age at the time of ALL diagnosis, and c) cytogenetics of the leukemia cells. The assigned risk level is then used to determine appropriate treatment intensity. Additionally, a subgroup of participants with ALL—only those on specific POG treatment protocols—were randomized to receive one of two different dosage levels of intravenous methotrexate (IVMTX)—either $1\text{g}/\text{m}^2$ or $2\text{g}/\text{m}^2$. Other participants with ALL received either $100\text{mg}/\text{m}^2/\text{day}$ or $2.5\text{mg}/\text{m}^2$ of IVMTX, depending on their assigned POG protocol.

Newly diagnosed English-speaking children, between the ages of 3 years and 13 years, 11 months were invited to participate in the investigation. Exclusion criteria for participation were the following: (a) a diagnosis of at least one of the following: mental retardation ($\text{FSIQ} < 70$), specific learning disability or related learning disorder, or attention deficit/hyperactivity disorder or (b) history of neurological disorder, psychiatric disorder, or traumatic brain injury associated with an alteration of consciousness.

Recruitment occurred within the first 100 weeks of the study. Parents of potential participants with ALL were provided information about the study by the oncologist or nurse practitioner in charge of their child's care. Additionally, children who were old enough to assent were included in this initial discussion. Families who were interested in participation were then referred to the site Principal Investigator (PI) who worked with the attending oncology team to describe the procedures involved in participation, as well

as the potential risks and benefits of participation. A total of 88 participants with ALL were recruited from the two participating institutions (21 from the University of Arizona College of Medicine and 67 from the Texas Children's Cancer Center); 4 participants of the 88 recruited failed to participate in any of the cognitive evaluations. This reduced the total number of participants to 84, of which 64 (76.2%) participants were from the Baylor College of Medicine and 20 (23.8%) were from the University of Arizona. This final sample of ALL participants was composed of 35 (41.7%) females and 49 (58.3%) males. The ethnic breakdown of the study's sample with ALL was: 38 (45.2%) Caucasian, 19 (22.6%) Hispanic, 5 (6%) African American, 1 (1.2%) Asian American, 1 (1.2%) Native American, and 11 (13.1%) multiracial. Ethnicity data for a total of 9 (10.7%) participants was unreported.

At 1 to 2 months post-diagnosis of ALL, the PI again approached those families with more than one child in order to discuss the possibility of including the sibling(s) in the study. At this time, parents and siblings old enough to assent were informed of the participation procedures as well as any associated risks and benefits. A total of 22 non-ALL sibling participants were recruited from the two participating institutions (18 from the University of Arizona College of Medicine and 4 from the Texas Children's Cancer Center). Written informed consent was obtained prior to participation; 1 of which failed to complete the initial cognitive evaluation. This reduced the total number of non-ALL sibling participants to 21, of which 3 (14.3%) participated through the Baylor College of Medicine and 18 (85.7%) participated through the University of Arizona. Sibling participants are a useful comparison group because their performance over time on

dependent measures can be representative of what would be typically expected from the ALL participants had they not been diagnosed with and treated for leukemia.

In the present study, data from all 21 non-ALL siblings was utilized (see Table 1). Of the original 84 participants with ALL, data from 8 participants were excluded from present analyses because the participants did not meet one or both of the following criteria: (a) were not treated with either 1g/m² or 2g/m² of IVMTX and b) did not complete at least the initial cognitive evaluation. The addition of these latter criteria resulted in a final sample size of 76 participants with ALL (see Table 2).

Materials

Global intelligence was measured using composite scores from the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) and the Wechsler Preschool and Primary Scale of Intelligence—Revised (WPPSI-R; Wechsler, 1989). The WASI was administered to children aged 6 years old and older. The WPPSI-R was administered to children between the ages of 3 years and 5 years, 11 months. Each measure yielded the following composite scores: a Full Scale IQ (FSIQ) standard score, a Verbal IQ (VIQ) standard score, and a Performance IQ (PIQ) standard score. Standard scores have a mean of 100 and a standard deviation of 15. The WASI was comprised of four subtests: Vocabulary and Similarities (which contributed to the VIQ as well as FSIQ), and Block Design and Matrix Reasoning (which contributed to the PIQ as well as FSIQ). Average reliability coefficients for the WASI subtests ranged from 0.87 to 0.92, and reliability coefficients for the WASI FSIQ, VIQ, and PIQ were 0.86, 0.93, and 0.94, respectively (Wechsler, 1999). The WPPSI-R FSIQ, VIQ, and PIQ had average reliability coefficients

Table 1

Characteristics of Study's Non-ALL Sibling Participants

Total Sample Size (N) = 21		
Sample Characteristics	N	%
Gender		
Females	16	76.2
Males	5	23.8
Ethnicity		
Caucasian	10	47.6
Hispanic	6	28.6
African American	0	0.0
Asian American	0	0.0
Native American	2	9.5
Multiracial	2	9.5
Unreported	1	4.8
Age Category		
< 5 years old	1	4.8
≥ 5 years old	20	95.2
Dominant Handedness		
Right	17	81.0
Left	4	19.0
Maternal Education Level		
Less than high school or equivalent	0	0.0
High school or equivalent	12	57.1
College	7	33.3
Graduate/Professional school	1	4.8
Unreported	1	4.8

of 0.96, 0.95, and 0.92, respectively. The subtests contributing to these composites included Vocabulary, Similarities, Information, Comprehension, and Arithmetic (VIQ and FSIQ), and Block Design, Object Assembly, Geometric Design, Mazes and Picture

Table 2

Characteristics of Study's ALL Participants

Total Sample Size (N) = 76		
Sample Characteristics	N	%
Gender		
Females	44	57.9
Males	32	42.1
Ethnicity		
Caucasian	36	47.4
Hispanic	17	22.4
African American	4	5.3
Asian American	1	1.3
Native American	1	1.3
Multiracial	10	13.2
Unreported	7	9.2
Age Category		
< 5 years old	22	28.9
≥ 5 years old	54	71.1
Dominant Handedness		
Right	65	85.5
Left	11	14.5
Maternal Education Level		
Less than high school or equivalent	7	9.2
High school or equivalent	23	30.3
College	31	40.8
Graduate/Professional school	4	5.3
Unreported	11	14.5
ALL Risk Level		
Low Risk	33	43.4
Standard Risk	39	51.3
High Risk	4	5.3
ALL Treatment		
1g/m ² IVMTX	54	71.1
2g/m ² IVMTX	22	28.9

Completion (PIQ and FSIQ). Average reliability coefficients for these subtests ranged from 0.63 to 0.86 (Wechsler, 1989).

Language was assessed with scores from three different measures, including the Vocabulary and Similarities subtests from the WASI (Wechsler, 1999)/WPPSI-R (Wechsler, 1989) and scores from the Peabody Picture Vocabulary Test—Third Edition (PPVT-III; Dunn & Dunn, 1997). On the subtests from the WASI and WPPSI-R participants were required to provide word definitions and tell how two objects or concepts are alike. Performance on these measures is indicative of skills such as verbal concept formation and fund of knowledge (Sattler, 2001). Each of these subtests yielded a scaled score with a mean of 10 and a standard deviation of 3. The PPVT-III is a measure of receptive vocabulary and required participants to choose one of four pictures that best depicted a given word. This measure yielded a standard score with a mean of 100 and a standard deviation of 15 and had a reliability coefficient of 0.95 (Dunn & Dunn, 1997).

Visual-spatial/visual-motor skills were measured by scores from the Developmental Test of Visual Motor Integration—Fourth Edition (VMI; Beery, 1997) and the Block Design subtest from the WASI (Wechsler, 1999)/WPPSI-R (Wechsler, 1989). The VMI is a paper and pencil measure that required each participant to reproduce increasingly complex figures through coordination of visual perception and fine motor movement. This measure had a split-half reliability coefficient of 0.78 and yielded a standard score with a mean of 100 and a standard deviation of 15. Participant enrollment in a separate mathematics intervention study (initiated after Assessment II data was

collected), which had the potential to impact performance scores on these measures, resulted in the removal of Assessment III and Assessment IV scores of those participants receiving 10 or more hours of mathematics intervention from the analysis of VMI performance. The subtest from the WASI and WPPSI-R required the participants to perform many tasks such as reproducing two-dimensional designs with colored blocks within a specified time limit. The average reliability coefficient for the Block Design (WPPSI-R) subtest was 0.85. This subtest yielded scaled scores with a mean of 10 and a standard deviation of 3 for each participant. Performance on these subtests measures skills including nonverbal concept formation, perceptual organization, spatial visualization, abstract conceptualization, planning ability, and visual discrimination (Sattler, 2001).

Attention and working memory were measured by scores from four separate measures including the Arithmetic subtest from both the WPPSI-R (Wechsler, 1989) and the WISC-III (Wechsler, 1991); the Bead Memory and Memory for Sentences subtests from the Stanford-Binet Intelligence Scales—Fourth Edition (SB-IV; Thorndike et al., 1986a); and the WISC-III Digit Span subtest and Freedom from Distractibility Index (FDI) score, only for those children whose age allowed administration of this measure at Assessment I. The Arithmetic subtest from the WISC-III and WPPSI-R yielded a scaled score with a mean of 10 and a standard deviation of 3 and had average reliability coefficients ranging from 0.78 to 0.80. This subtest required participants to mentally solve arithmetic problems that were read aloud. Performance on this subtest is indicative of facility with mental arithmetic, numerical reasoning ability, and other abilities such as

concentration, attention, and short-term and working memory (Sattler, 2001). The WISC-III Digit Span subtest yielded a scaled score with a mean of 10 and a standard deviation of 3 and had average reliability coefficients ranging from 0.79 to 0.91. On this measure, the participants were required to repeat series of digits read aloud. Performance is indicative of short-term sequential auditory memory and attention (Sattler, 2001). The Arithmetic and Digit Span subtests combine to yield the WISC-III FDI score, which was presented as a standard score with a mean of 100 and a standard deviation of 15 (Sattler, 2001). The measures from the SB-IV yielded z-scores with a mean of 0 and a standard deviation of 1.0 and had average reliability coefficients ranging from 0.87 to 0.89 (Thorndike, Hagen, & Sattler, 1986b). On these subtests, participants were required to reconstruct designs from memory using beads of various color and shape, and to repeat sentences of increasing length and complexity. Performance on these subtests is indicative of attention, concentration, fluid ability, freedom from distractibility, sequencing, and short-term and working memory (Sattler, 2001).

Processing speed was measured for a subset of the sample—only those participants whose age allowed administration of the WISC-III beginning at Assessment I. Scaled scores (mean 10, standard deviation 3) from the Coding and Symbol Search subtests from the WISC-III (Wechsler, 1991) were used to represent processing speed. Additionally, these subtests were combined to yield a Processing Speed Index score (PSI) with a mean of 100 and a standard deviation of 15. These measures required participants to copy symbols according to a specified key, and to identify a target symbol among an array of distractor stimuli—each task is timed. Performance on these measures is

indicative of speed of mental operation and cognitive flexibility, but also involves skills such as visual motor coordination, attention, short-term memory, perceptual discrimination, and scanning and tracking (Sattler, 2001).

Psychomotor speed and coordination were measured using the standard score (mean 100, standard deviation 15) from the Purdue Pegboard Test (PPT; Tiffin, 1968). This measure required each participant to place as many rounded pegs into holes as possible within a specified time limit. This task was performed with the participant's dominant hand and non-dominant hand individually, and then again with both hands simultaneously. Each trial yielded a z -score with a mean of 0 and a standard deviation of 1.0. Average reliability coefficients for single trial administrations of the PPT have been shown to be as high as 0.82 (Tiffin, 1968).

Executive function was evaluated using the Behavioral Regulation Index (BRI), Metacognition Index (MI), and Global Executive Composite (GEC) scores from the Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000) for those participants who were rated on this measure beginning at Assessment I. Similarly, scores from the Matrix Reasoning subtest from the WASI (Wechsler, 1999) were analyzed only for the subset of the sample that was administered this measure beginning at Assessment I. Additionally, scores from the Similarities subtest of the WASI (Wechsler, 1999) and WPPSI-R (Wechsler, 1989) were used for all participants. Performance on measures of executive function is indicative of the ability to manage novel and unfamiliar circumstances, develop strategies, and monitor effectiveness (Shallice, 1990) or higher order problem solving abilities. The BRIEF was completed by each participant's parent

and yielded *T*-scores with a mean of 50 and a standard deviation of 10. *T*-scores were obtained for the following clinical scales: Inhibit, Shift, Emotional Control, Initiate (all of which contributed to the BRI score), and Working Memory, Plan/Organize, Organization of Materials, and Monitor (all of which contributed to the MI score); the BRI and MI scores combined to yield the GEC. The average reliability coefficients on this measure ranged from 0.81 to 0.98 (Strauss, Sherman, & Spreen, 2006). The Matrix Reasoning and Similarities subtests required superordinate verbal concept formation and higher order non-verbal reasoning skills, respectively. These subtests yielded scaled scores with a mean of 10 and a standard deviation of 3 and had average reliability coefficients between 0.87 and 0.92 (Wechsler, 1999).

Academic achievement was measured using the Letter-Word Identification, Dictation, Calculation, and Applied Problems subtests from the Woodcock-Johnson Psychoeducational Battery—Revised, Tests of Achievement (WJ-R ACH; Woodcock & Johnson, 1989), which yielded standard scores with a mean of 100 and a standard deviation of 15. Two forms of this measure were alternated between each year of assessment to avoid practice effects. These subtests involved skills such as reading aloud single letters and words (Mather & Jaffee, 2002), writing and spelling words, along with using punctuation and capitalization accurately (Spreen & Strauss, 1998), and retrieving math facts and performing mathematical calculations based on written and orally presented problems (Mather & Jaffee, 2002). The split-half reliability coefficients for these subtests all exceed 0.80 (Woodcock & Mather, 1989). Performance on these subtests is indicative of basic academic skills in the areas of reading, writing/spelling, and

mathematics. Participant enrollment in a separate mathematics intervention study that began after Assessment II, and which had the potential to impact performance scores on these measures, was considered in statistical analyses. In this regard, scores of participants receiving 10 or more hours of mathematics intervention were removed from analyses beyond Assessment II.

Social-emotional/behavioral function was measured based on the scores from the Behavior Assessment System for Children (BASC)—Parent Report Form (PRF; Reynolds & Kamphaus, 1993), which yielded composite scores in the areas of Behavioral Symptoms, Adaptive Skills, Internalizing Behaviors, Externalizing Behaviors. These composites are based on scores in the following clinical areas: Hyperactivity, Aggression, Conduct Problems, Anxiety, Depression, Somatization, Atypicality, Withdrawal, Attention Problems, Adaptability, Social Skills, and Leadership. These scores had reliability coefficients ranging from 0.70 to the low 0.90s (Reynolds & Kamphaus, 1993). Additionally, scores from the BASC—Self-Report of Personality (SRP; Reynolds & Kamphaus, 1993), which was administered to children 8 years old and older, was analyzed for those participants who completed this measure beginning at Assessment I. This measure is a child-completed rating scale and contains questions in the following clinical areas: Attitude to School, Attitude to Teachers, Atypicality, Locus of Control, Social Stress, Anxiety, Depression, Sense of Inadequacy, Relations with Parents, Interpersonal Relations, Self-Esteem, Self Reliance, Sensation Seeking, and Somatization and yielded composite scores for the following domains: School Maladjustment, Clinical Maladjustment, Personal Adjustment, and Emotional Symptoms. The reliability

coefficients for these scales ranged from 0.70 to the mid 0.90s (Reynolds & Kamphaus, 1993). Table 3 shows the measures utilized as part of the current investigation.

Design and Procedure

Cognitive evaluations were conducted in the Pediatric Neuropsychology Clinic at the University of Arizona Health Sciences Center and The Learning Center at the Baylor College of Medicine. Families interested in participating were contacted via telephone regarding their child's availability for the initial cognitive evaluation. The initial evaluation (Assessment I) occurred between days 15 and 28 of treatment. ALL participants had two CNS/intrathecal treatments prior to the initial evaluation (occurring on days 1 and 15) and then participated in Assessment I when they were physiologically stable. Initial evaluations (Assessment I) were completed during the remission induction phase of treatment—prior to each child's initial treatment with intermediate dose intravenous methotrexate (IVMTX). This order of procedure was important as this medication has been shown to cross the blood-brain barrier and thus is thought to impact cognitive functioning (Shuper et al., 2000) and because the dosage level of IVMTX was an experimental variable in the previous investigation. The dose of IVMTX received by each participant was determined by random assignment procedure. Through this procedure, two groups were created, one of which received 1 gm/m² and another that received 2gm/m² of IVMTX. Participants were invited to return for three additional annual cognitive evaluations. Assessment II was conducted approximately 12 months post-Assessment I (during the maintenance stage of treatment), Assessment III was conducted approximately 24 months post-Assessment I (during the maintenance stage of

Table 3

Measures Utilized in the Current Investigation

Measure	Type of Score(s) Yielded	Score Mean (Standard Deviation)
Wechsler Abbreviated Scale of Intelligence (WASI) ^b	Standard Scores	100(15)
Wechsler Preschool and Primary Scales of Intelligence—Revised (WPPSI-R) ^c	Standard Scores	100(15)
Wechsler Intelligence Scale for Children—3 rd Edition (WISC-III) ^b	Standard Scores (composites) Scaled Scores (subtests)	100(15) 10(3)
Peabody Picture Vocabulary Test (PPVT-III) ^a	Standard Score	100(15)
Developmental Test of Visual Motor Integration—4 th Edition (VMI) ^a	Standard Score	100(15)
Woodcock-Johnson Psychoeducational Battery—Revised, Tests of Achievement (WJ-R ACH) ^a	Standard Score	100(15)
Stanford Binet Intelligence Scales—4 th Edition (SB-IV) ^a	Z scores	0(1.0)
Purdue Pegboard Test (PPT) ^a	Z scores	0(1.0)
Behavior Regulation Inventory of Executive Functioning (BRIEF) ^e	T scores	50(10)
Behavior Assessment Scale for Children, Parent Report Form (BASC-PRF) ^e	T scores	50(10)
Behavior Assessment Scale for Children—Self Report of Personality (BASC-SRP) ^d	T scores	50(10)

^a measures administered to all participants

^b measures administered to participants ≥ 6 years of age only

^c measures administered to participants < 6 years of age only

^d measures administered to participants ≥ 8 years of age only

^e measure completed by participant's parent/guardian

treatment), and finally, Assessment IV was conducted approximately 36 months post-Assessment I (after treatment completion).

The cognitive evaluation included several tests administered at Assessments I through IV in the following fixed order: PPVT-III, VMI, WASI/WISC-III/WPPSI-R, WJ-R ACH (Letter-Word, Calculation, Applied Problems, Dictation), COWA, SB-IV (Sentence Memory, Bead Memory), and PPT. Scores from the COWA were not analyzed as part of this study due to the unavailability of norms for all subtests for each age group participating in this study. Administration of the KeyMath-R measure, initiated at Assessment II, followed an alternating procedure (Form A used for Assessments II and IV, and Form B used for Assessment III). Additionally, this measure was included as a dependent measure for a subset of the ALL sample that participated in an intervention study and thus results from the KeyMath-R were not analyzed in the present study as it was possible the intervention differentially impacted performance on this measure. This entire battery of tests was administered to each child and scored according to manualized instructions by a neuropsychology postdoctoral fellow, one other graduate student, and the present researcher. Parents completed rating scales, the BRIEF and the PRF, designed to measure executive function and social-emotional/behavioral function in their child, while their child was participating in the cognitive evaluation. Parents were also asked to complete a demographic information questionnaire that requested information regarding the child's age at diagnosis, gender, the family's socioeconomic status (SES), the child's school attendance, and baseline cognitive and academic abilities. Parental education and employment information was also requested.

Each participant or participant's parent was given \$50 for participation and parking fees were paid. Feedback related to the findings of the cognitive evaluation was provided in a brief report format to each participant's parents. If the parents had any questions regarding the findings they were encouraged to call the respective testing site at which they were evaluated. If elevated scores were noted on the measure of social-emotional/behavioral function, specifically in the areas of depression and anxiety, these findings were reported to the family, the chief neuropsychologist overseeing the cognitive evaluations, the PI and the Institutional Review Board (IRB).

Scores from the cognitive evaluation and parent rating scales were entered into a database. Demographic information were sanitized of all identifying information (each participant was assigned a unique identification number) and coded and entered into the database alongside each participant's cognitive evaluation data. Information contained within this database was analyzed in the current study.

Analysis of Findings

Consistent with the stated hypotheses, several statistical analyses were performed using SPSS 17.0 for Mac. Analyses of *a priori* hypotheses were conducted using Bonferroni adjusted alpha levels (ranging from 0.010 to 0.025 based on the number of analyses conducted per domain of functioning) applied to all tests. Specifically, analyses for measures of global intelligence, language function, processing speed, psychomotor speed and coordination, and executive function were performed using an alpha level of 0.017; visual-spatial/visual-motor function using an alpha level of 0.025; attention and working memory function using an alpha level of 0.010; academic achievement and

social-emotional/behavioral function using an alpha level of 0.013. Additionally, *post hoc* simple pairwise comparisons were also conducted at an alpha level of 0.05 with the Bonferroni correction applied to control the family-wise error rate.

Statistical analyses were conducted using linear mixed model designs. For analyses examining only participants with ALL, the independent variables of group (i.e., 1g/m² vs. 2g/m²), time (Assessments I, II, III, and IV), and age at diagnosis (< 5 years old vs. ≥ 5 years old) were entered into the model as fixed factors. The analysis of the main effect for age at diagnosis and of the interaction effect for age at diagnosis x time were not performed for those dependent measures which were not administered at Assessment I due to participant age requirements. These restrictions affected the analyses of the WISC-III FDI and PSI composites and Coding, Symbol Search, and Digit Span subtests, the WASI Matrix Reasoning subtest, the BASC-SRP, and the BRIEF. Analyses produced *F* test values for each main effect and for the interaction effects of group x time and age at diagnosis x time.

For analyses examining participants with ALL and non-ALL sibling participants, independent variables entered into the model as fixed factors included: group (i.e., ALL vs. non-ALL sibling), and time (Assessments I, II, III, and IV). Analyses produced *F* test values for each main effect and for the interaction effect of group x time. Although age at diagnosis was not included in the analyses of ALL and sibling participants, data from participants who were not administered the WISC-III FDI and PSI composites and Coding, Symbol Search, and Digit Span subtests, the WASI Matrix Reasoning subtest,

the BASC-SRP, and the BRIEF measures at Assessment I were excluded from analyses as having “baseline” scores on these measures was important to the current study.

Maternal education level was used as a blocking variable in all analyses related to each hypothesis as research has shown maternal education level to be positively related to children’s intelligence scores (Breslau et al., 2001).

CHAPTER 4

RESULTS

This chapter examines each of the hypotheses tested and reports the results, indicating where statistically significant differences in performance on measures of cognitive, academic, and social-emotional/behavioral functioning were identified due to (a) the main effect of group membership (i.e., ALL 1g/m² versus ALL 2g/m² or ALL total versus non-ALL siblings), (b) the main effect of time (i.e., evaluation number), (c) the main effect of age at diagnosis (for ALL participants only), (d) the interaction effect of group membership and time, and (f) the interaction effect of age at diagnosis and time (for ALL participants only).

Hypothesis I-Participants with ALL will not differ significantly on measures of global intelligence

On the WASI/WPPSI-R Full Scale IQ composite (FSIQ), the analysis revealed no significant main effect for group $F(1,77) = 0.123, p = 0.726$, time $F(3,149) = 0.040, p = 0.989$, or age at diagnosis $F(1,72) = 0.006, p = 0.936$. Additionally, no significant interaction effect for group x time $F(3,150) = 0.195, p = 0.900$, or age x time $F(3,147) = 0.620, p = 0.603$ was observed.

The analysis of performance of participants with ALL on the WASI/WPPSI-R Verbal IQ composite (VIQ) revealed no significant main effect for group $F(1,78) = 0.689, p = 0.409$, time $F(3,150) = 0.241, p = 0.868$, or age at diagnosis $F(1,72) = 0.045, p = 0.833$. Additionally, no significant interaction effect for group x time $F(3,150) = 0.424, p = 0.736$, or age x time $F(3,147) = 0.366, p = 0.778$ was observed.

The analysis of performance of participants with ALL on the WASI/WPPSI-R Performance IQ composite (PIQ) revealed no significant main effect for group $F(1,76) = 0.081, p = 0.776$, time $F(3,148) = 0.040, p = 0.989$, or age at diagnosis $F(1,70) = 0.004, p = 0.947$. Additionally, no significant interaction effect for group x time $F(3,149) = 0.040, p = 0.989$, or age x time $F(3,145) = 0.544, p = 0.653$ was observed.

Hypothesis II-Participants with ALL will not differ significantly on measures of language function

The analysis of performance of participants with ALL on the Peabody Picture Vocabulary Test (PPVT-III) revealed no significant main effect for group $F(1,78) = 2.460, p = 0.121$, time $F(3,150) = 0.598, p = 0.617$, or age at diagnosis $F(1,73) = 2.403, p = 0.125$. Additionally, no significant interaction effect for group x time $F(3,150) = 0.351, p = 0.789$, or age x time $F(3,148) = 1.101, p = 0.351$ was observed.

The analysis of performance of participants with ALL on the WASI/WPPSI-R Vocabulary subtest revealed no significant main effect for group $F(1,80) = 2.388, p = 0.126$, time $F(3,152) = 0.175, p = 0.913$, or age at diagnosis $F(1,73) = 0.002, p = 0.961$. Additionally, no significant interaction effect for group x time $F(3,153) = 0.280, p = 0.840$, or age x time $F(3,149) = 0.027, p = 0.994$ was observed.

The analysis of performance of participants with ALL on the WASI/WPPSI-R Similarities subtest revealed no significant main effect for group $F(1,77) = 0.152, p = 0.697$, time $F(3,150) = 1.133, p = 0.338$, or age at diagnosis $F(1,71) = 0.092, p = 0.763$. Additionally, no significant interaction effect for group x time $F(3,150) = 0.495, p = 0.686$, or age x time $F(3,147) = 1.445, p = 0.232$ was observed.

Hypothesis III-Participants with ALL will not differ significantly on measures of visual-spatial/visual-motor function

The analysis of performance of participants with ALL on the WASI/WPPSI-R Block Design subtest revealed no significant main effect for group $F(1,77) = 0.204, p = 0.652$, time $F(3,149) = 0.638, p = 0.592$, or age at diagnosis $F(1,71) = 0.271, p = 0.605$. Additionally, no significant interaction effect for group x time $F(3,150) = 0.419, p = 0.740$, or age x time $F(3,146) = 2.034, p = 0.112$ was observed.

The analysis of performance of participants with ALL on the VMI revealed no significant effect for group $F(1,80) = 1.489, p = 0.226$, time $F(3,135) = 2.778, p = 0.044$, or age at diagnosis $F(1,73) = 0.449, p = 0.505$. Additionally, no significant interaction effect for group x time $F(3,137) = 0.149, p = 0.930$, or age x time $F(3,132) = 0.373, p = 0.772$ was observed.

Hypothesis IV-Participants with ALL will not differ significantly on measures of attention and working memory function

The analysis of performance of participants with ALL on the WISC-III Freedom From Distractibility Index (FDI) revealed no significant main effect for group $F(1,48) = 0.196, p = 0.660$, or time $F(3,85) = 1.460, p = 0.231$. Additionally, no significant interaction effect for group x time $F(3,79) = 3.137, p = 0.030$ was observed.

On the WISC-III Digit Span subtest, analysis revealed no significant main effect for group $F(1,52) = 0.003, p = 0.959$, or time $F(3,95) = 2.311, p = 0.081$. Additionally, no significant interaction effect for group x time $F(3,95) = 1.581, p = 0.199$ was observed.

The analysis of performance of participants with ALL on the WISC-III/WPPSI-R Arithmetic subtest revealed no significant main effect for group $F(1,75) = 0.038, p = 0.847$, time $F(3,148) = 0.257, p = 0.856$, or age at diagnosis $F(1,69) = 0.369, p = 0.546$. Additionally, no significant interaction effect for group x time $F(3,150) = 0.720, p = 0.542$, or age x time $F(3,145) = 0.488, p = 0.691$ was observed.

The analysis of performance of participants with ALL on the SB-IV Bead Memory subtest revealed a significant main effect for age at diagnosis $F(1,71) = 7.324, p = 0.009$ with participants less than 5 years of age at diagnosis ($M = -0.618, SD = 0.188$) performing significantly worse on this measure than did those participants who were 5 years of age or older at diagnosis ($M = -0.089, SD = 0.150, p = 0.009$). No significant main effect for group $F(1,78) = 0.138, p = 0.711$ or time $F(3,153) = 0.957, p = 0.415$ was observed. Additionally, no significant interaction effects were observed for group x time $F(3,154) = 2.867, p = 0.038$ or age x time $F(3,149) = 0.892, p = 0.447$.

On the SB-IV Sentence Memory subtest, analysis revealed no significant main effect for group $F(1,78) = 0.575, p = 0.451$, time $F(3,151) = 0.726, p = 0.538$, or age at diagnosis $F(1,72) = 0.222, p = 0.639$. Additionally, no significant interaction effect for group x time $F(3,152) = 1.370, p = 0.254$, or age x time $F(3,148) = 1.124, p = 0.341$ was observed.

Hypothesis V-Participants with ALL will not differ significantly on measures of processing speed

The analysis of performance on the WISC-III Processing Speed Index (PSI) revealed no significant main effect for group $F(1,50) = 0.029, p = 0.866$, or time $F(3,93)$

= 0.829, $p = 0.481$. Additionally, no significant interaction effect for group x time $F(3,93) = 0.403$, $p = 0.751$ was observed.

On the WISC-III Coding subtest no significant main effect for group $F(1,50) = 0.088$, $p = 0.768$, or time $F(3,94) = 0.487$, $p = 0.692$ was observed. Additionally, no significant interaction effect for group x time $F(3,94) = 0.656$, $p = 0.581$ was observed.

Additionally, analyses of participant performance on the WISC-III Symbol Search subtest revealed no significant main effect for group $F(1,51) = 0.007$, $p = 0.934$, or time $F(3,95) = 0.638$, $p = 0.593$. No significant interaction effect for group x time $F(3,95) = 0.290$, $p = 0.833$ was observed.

Hypothesis VI-Participants with ALL will not differ significantly on measures of psychomotor speed and coordination

The analysis of performance on the Purdue Pegboard Test (PPT) dominant hand trial revealed no significant main effect for group $F(1,79) = 0.023$, $p = 0.879$, time $F(3,154) = 0.325$, $p = 0.807$, or age at diagnosis $F(1,71) = 0.028$, $p = 0.867$. Additionally, no significant interaction effect for group x time $F(3,156) = 0.365$, $p = 0.779$, or age x time $F(3,150) = 0.941$, $p = 0.422$ was observed for the dominant hand trial.

Analysis of performance on the PPT non-dominant hand trial revealed no significant main effect for group $F(1,80) = 0.017$, $p = 0.898$, time $F(3,153) = 1.511$, $p = 0.214$, or age at diagnosis $F(1,74) = 0.092$, $p = 0.763$. Additionally, no significant interaction effect for group x time $F(3,155) = 0.348$, $p = 0.557$, or age x time $F(3,150) = 0.199$, $p = 0.897$ was observed.

On the PPT both hands trial, no significant main effect for group $F(1,82) = 0.348$, $p = 0.557$, time $F(3,153) = 0.599$, $p = 0.617$, or age at diagnosis $F(1,75) = 0.000$, $p = 0.983$. Additionally, no significant interaction effect for group x time $F(3,155) = 0.196$, $p = 0.899$, or age x time $F(3,150) = 0.443$, $p = 0.722$ was observed.

Hypothesis VII-Participants with ALL will not differ significantly on measures of executive function

The analysis of performance of participants with ALL on the WASI Matrix Reasoning subtest revealed no significant main effect for group $F(1,48) = 0.105$, $p = 0.747$, or time $F(3,89) = 0.794$, $p = 0.501$. Additionally, no significant interaction effect for group x time $F(3,89) = 0.494$, $p = 0.688$ was observed.

On the WASI Similarities subtest, analysis of performance revealed no significant main or interaction effects, as presented under Hypothesis II above.

Analysis of performance on the BRIEF Behavioral Regulation Index (BRI) revealed no significant main effect for group $F(1,47) = 1.728$, $p = 0.195$, or time $F(3,70) = 0.205$, $p = 0.893$. Additionally, no significant interaction effect for group x time $F(3,70) = 1.607$, $p = 0.196$ was observed.

On the BRIEF Metacognition Index (MI), no significant main effect for group $F(1,46) = 0.964$, $p = 0.331$, or time $F(3,67) = 1.221$, $p = 0.309$ was observed. Additionally, no significant interaction effect for group x time $F(3,67) = 1.779$, $p = 0.160$ was observed.

Analysis of performance on the BRIEF Global Executive Composite (GEC) revealed no significant main effect for group $F(1,46) = 1.325$, $p = 0.256$, or time $F(3,67)$

= 0.551, $p = 0.649$. Additionally, no significant interaction effect for group x time $F(3,67) = 1.804$, $p = 0.155$ was observed.

Hypothesis VIII-Participants with ALL will not differ significantly on measures of academic achievement

The analysis of performance on the WJ-R Letter Word subtest revealed no significant main effect for group $F(1,83) = 0.000$, $p = 1.000$, time $F(3,156) = 3.667$, $p = 0.014$, or age at diagnosis $F(1,77) = 5.183$, $p = 0.026$. Additionally, no significant interaction effect for group x time $F(3,156) = 2.393$, $p = 0.071$, or age x time $F(3,152) = 0.314$, $p = 0.815$ was observed.

The analysis of performance of participants with ALL on the WJ-R Dictation subtest revealed a significant main effect of age at diagnosis $F(1,71) = 6.850$, $p = 0.011$ with participants who were less than 5 years of age at diagnosis ($M = 99.012$, $SD = 3.063$) performing significantly better than participants who were 5 years of age and older at diagnosis ($M = 90.626$, $SD = 2.402$, $p = 0.011$). No significant main effect for group $F(1,77) = 0.402$, $p = 0.528$, or time $F(3,149) = 0.865$, $p = 0.461$ was noted. Additionally, no significant interaction effect for group x time $F(3,150) = 0.361$, $p = 0.781$, or age x time $F(3,147) = 3.483$, $p = 0.018$ was observed.

The analysis of performance of participants on the WJ-R Calculation subtest revealed no significant main effect for group $F(1,58) = 0.660$, $p = 0.420$, time $F(3,115) = 2.059$, $p = 0.109$, or age at diagnosis $F(1,77) = 0.805$, $p = 0.372$. Additionally, no significant interaction effect for group x time $F(3,83) = 0.091$, $p = 0.965$, or age x time $F(3,100) = 1.939$, $p = 0.149$ was observed.

The analysis of performance on the WJ-R Applied Problems subtest revealed no significant main effect for group $F(1,76) = 0.175, p = 0.677$, time $F(3,126) = 1.050, p = 0.373$, or age at diagnosis $F(1,71) = 0.219, p = 0.641$. Additionally, no significant interaction effect for group x time $F(3,127) = 0.771, p = 0.512$, or age x time $F(3,124) = 0.944, p = 0.422$ was observed.

Hypothesis IX-Participants with ALL will not differ significantly on measures of social-emotional/behavioral function

The analysis of performance on the BASC-PRF Behavioral Symptoms composite revealed no significant main effect for group $F(1,68) = 0.024, p = 0.878$, time $F(3,108) = 0.423, p = 0.737$, or age at diagnosis $F(1,63) = 0.118, p = 0.732$. Additionally, no significant interaction effect for group x time $F(3,109) = 1.906, p = 0.133$, or age x time $F(3,106) = 2.439, p = 0.069$ was observed.

The analysis of performance on the BASC-PRF Adaptive Skills composite revealed a significant main effect for treatment group $F(1,70) = 7.486, p = 0.008$; participants treated with 1gm/m^2 of IVMTX ($M = 50.076, SD = 1.558$) were rated significantly worse than the participants treated with 2gm/m^2 of IVTMX ($M = 56.543, SD = 2.481, p = 0.008$). No significant main effect for time $F(3,127) = 0.492, p = 0.689$, or age at diagnosis $F(1,61) = 0.414, p = 0.522$ was noted. Additionally, no significant interaction effect for group x time $F(3,105) = 0.962, p = 0.414$, or age x time $F(3,100) = 0.157, p = 0.925$ was observed.

The analysis of performance of participants with ALL on the BASC-PRF Internalizing Symptoms composite revealed no significant main effect for group $F(1,71)$

= 0.288, $p = 0.593$, time $F(3,114) = 2.471$, $p = 0.065$, or age at diagnosis $F(1,64) = 0.136$, $p = 0.713$. Additionally, no significant interaction effect for group x time $F(3,115) = 0.974$, $p = 0.407$, or age x time $F(3,111) = 1.530$, $p = 0.211$ was observed.

The analysis of performance of participants with ALL on the BASC-PRF Externalizing Symptoms composite revealed no significant main effect for group $F(1,70) = 0.006$, $p = 0.940$, time $F(3,111) = 0.990$, $p = 0.400$, or age at diagnosis $F(1,64) = 0.420$, $p = 0.520$. Additionally, no significant interaction effect for group x time $F(3,112) = 1.508$, $p = 0.216$, or age x time $F(3,109) = 1.827$, $p = 0.147$ was observed.

The analysis of performance on the BASC-SRP Emotional Symptoms composite revealed no significant main effect for group $F(1,34) = 0.000$, $p = 0.995$, or time $F(3,51) = 0.121$, $p = 0.947$. Additionally, no significant interaction effect for group x time $F(3,51) = 1.467$, $p = 0.234$ was observed.

On the BASC-SRP Personal Adjustment composite, no significant main effect for group $F(1,28) = 0.080$, $p = 0.780$, or time $F(3,48) = 0.071$, $p = 0.975$. Additionally, no significant interaction effect for group x time $F(3,49) = 0.649$, $p = 0.587$ was observed.

On the BASC-SRP Clinical Maladjustment composite, no significant main effect for group $F(1,35) = 0.033$, $p = 0.858$, or time $F(3,46) = 0.442$, $p = 0.724$. Additionally, no significant interaction effect for group x time $F(3,47) = 2.011$, $p = 0.125$ was observed.

On the BASC-SRP School Maladjustment composite, no significant main effect for group $F(1,29) = 2.425$, $p = 0.130$, or time $F(3,46) = 1.287$, $p = 0.290$ was noted. Additionally, no significant interaction effect for group x time $F(3,46) = 1.980$, $p = 0.130$ was observed.

Hypothesis X-There will be no significant main effect of age at diagnosis on performance of participants with ALL on measures of cognitive, academic, and social-emotional/behavioral functioning

The analysis of performance on the WJ-R Dictation subtest revealed a significant main effect of age at diagnosis $F(1,71) = 6.850, p = 0.011$ with participants who were less than 5 years of age at diagnosis ($M = 99.012, SD = 3.063$) performing significantly better than participants who were 5 years of age and older at diagnosis ($M = 90.626, SD = 2.402, p = 0.011$).

The analysis of performance on the SB-IV Bead Memory subtest revealed a significant main effect for age at diagnosis $F(1,71) = 7.324, p = 0.009$ with participants less than 5 years of age at diagnosis ($M = -0.618, SD = 0.188$) performing significantly worse on this measure than did those participants who were 5 years of age or older at diagnosis ($M = -0.089, SD = 0.150, p = 0.009$).

Hypothesis XI-Participants with ALL and non-ALL siblings will not differ significantly on measures of cognitive functioning, academic achievement, and social-emotional/behavioral functioning

Analysis of performance on the WASI/WPPSI-R FSIQ, revealed no significant main effect for group $F(1,102) = 1.313, p = 0.255$, or time $F(3,190) = 1.087, p = 0.356$. Additionally, no significant interaction effect for group x time $F(3,190) = 1.264, p = 0.288$ was observed.

The analysis of performance on the WASI/WPPSI-R VIQ revealed no significant main effect for group $F(1,101) = 0.879, p = 0.351$, or time $F(3,190) = 0.914, p = 0.435$.

Additionally, no significant interaction effect for group x time $F(3,190) = 0.526, p = 0.665$ was observed.

On the WASI/WPPSI-R PIQ, no significant main effect for group $F(1,102) = 1.223, p = 0.271$, or time $F(3,191) = 1.222, p = 0.303$ was observed. Additionally, no significant interaction effect for group x time $F(3,191) = 2.184, p = 0.091$ was observed.

The analysis of performance on the PPVT-III revealed nonsignificant main effects were noted for group $F(1,103) = 0.053, p = 0.819$ and time $F(3,191) = 0.583, p = 0.627$. Additionally, no significant interaction effect for group x time $F(3,191) = 0.154, p = 0.927$ was observed.

On the WASI/WPPSI-R Vocabulary subtest no significant main effect for group $F(1,102) = 0.119, p = 0.731$, or time $F(3,192) = 0.334, p = 0.801$ was noted. Additionally, no significant interaction effect for group x time $F(3,192) = 0.257, p = 0.856$ was observed.

Similarly, on the WASI/WPPSI-R Similarities subtest no significant main effect for group $F(1,101) = 1.082, p = 0.301$, or time $F(3,191) = 1.848, p = 0.140$ was noted. Additionally, no significant interaction effect for group x time $F(3,191) = 0.127, p = 0.944$ was observed.

On the WASI/WPPSI-R Block Design subtest, no significant main effect for group $F(1,104) = 1.001, p = 0.319$, or time $F(3,193) = 0.467, p = 0.705$ was noted. Additionally, no significant interaction effect for group x time $F(3,193) = 1.060, p = 0.367$ was observed on this dependent measure.

Analysis of performance on the VMI revealed no significant main effect for group $F(1,99) = 5.015, p = 0.027$, or time $F(3,177) = 1.643, p = 0.181$. Additionally, no significant interaction effect for group x time $F(3,177) = 2.100, p = 0.102$ was observed on the VMI.

The analysis of performance means on the WISC-III FDI composite revealed no significant main effect for group $F(1,74) = 0.436, p = 0.511$, or time $F(3,132) = 2.737, p = 0.046$, and no significant interaction effect for group x time $F(3,118) = 0.373, p = 0.773$.

On the WISC-III Digit Span subtest, no significant main effect for group $F(1,77) = 0.035, p = 0.853$, or time $F(3,133) = 1.086, p = 0.358$ was observed. Additionally, no significant interaction effect for group x time $F(3,133) = 0.374, p = 0.772$ was observed.

The analysis of performance on the WISC-III/WPPSI-R Arithmetic subtest revealed no significant main effect for group $F(1,106) = 1.247, p = 0.267$ or time $F(3,194) = 0.634, p = 0.595$. Additionally, no significant interaction effect for group x time $F(3,194) = 0.427, p = 0.734$ was observed.

Similarly, analysis of performance on the SB-IV Bead Memory subtest revealed no significant main effect for group $F(1,103) = 1.633, p = 0.204$, or time $F(3,198) = 1.117, p = 0.343$, and no significant interaction effect for group x time $F(3,198) = 0.894, p = 0.445$.

On the SB-IV Sentence Memory subtest, no significant main effect for group $F(1,106) = 3.065, p = 0.083$, or time $F(3,195) = 1.707, p = 0.167$ was observed, nor was a significant interaction effect for group x time $F(3,195) = 0.546, p = 0.651$ noted.

The analysis of performance on the WISC-III PSI composite revealed no significant main effect for group $F(1,74) = 1.101, p = 0.297$, or time $F(3,129) = 0.316, p = 0.814$, and no significant interaction effect for group x time $F(3,129) = 0.207, p = 0.892$.

Similarly, no significant main effect for group $F(1,76) = 1.958, p = 0.166$, or time $F(3,132) = 0.413, p = 0.744$, and no significant interaction effect for group x time $F(3,132) = 0.274, p = 0.844$ was observed on WISC-III Coding subtest.

On the WISC-III Symbol Search subtest, no significant main effect for group $F(1,73) = 0.330, p = 0.567$, or time $F(3,130) = 0.096, p = 0.962$ was noted. Additionally, no significant interaction effect for group x time $F(3,129) = 0.412, p = 0.745$ was observed on this dependent measure.

The analysis of performance on the PPT dominant hand trial revealed no significant main effect for group $F(1,99) = 2.084, p = 0.152$, or time $F(3,199) = 0.035, p = 0.991$. Additionally, no significant interaction effect for group x time $F(3,199) = 0.913, p = 0.436$ was observed.

On the PPT non-dominant hand trial, there was no significant main effect for group $F(1,103) = 2.725, p = 0.102$, or time $F(3,198) = 0.150, p = 0.929$, and no significant interaction effect for group x time $F(3,198) = 1.346, p = 0.261$.

On the PPT both hands trial, no significant main effect for group $F(1,94) = 1.623, p = 0.206$ or time $F(3,184) = 0.847, p = 0.470$ was observed, nor was there a significant interaction effect for group x time $F(3,184) = 1.208, p = 0.308$.

Analysis of performance on the WASI/WPPSI-R Similarities subtest revealed no significant main effect for group $F(1,101) = 1.082, p = 0.301$, or time $F(3,191) = 1.848, p = 0.140$. Additionally, no significant interaction effect for group x time $F(3,191) = 0.127, p = 0.944$ was observed.

On the WASI Matrix Reasoning subtest, there was no significant main effect for group $F(1,70) = 0.663, p = 0.418$, or time $F(3,125) = 1.873, p = 0.144$, and no significant interaction effect for group x time $F(3,125) = 1.649, p = 0.182$.

On the BRIEF BRI composite, no significant main effect for group $F(1,62) = 0.995, p = 0.322$, or time $F(3,96) = 1.073, p = 0.364$ was observed. Additionally, no significant interaction effect for group x time $F(3,96) = 0.705, p = 0.552$ was noted.

On the BRIEF MI composite, no significant main effect for group $F(1,62) = 0.749, p = 0.390$, or time $F(3,92) = 0.284, p = 0.837$, and no significant interaction effect for group x time $F(3,93) = 1.379, p = 0.254$ was observed.

Finally, on the BRIEF GEC composite, there was no significant main effect for group $F(1,62) = 0.533, p = 0.468$, or time $F(3,92) = 0.134, p = 0.939$. Additionally, no significant interaction effect for group x time $F(3,92) = 0.655, p = 0.582$ was observed.

The analysis of performance of participants with ALL and non-ALL sibling participants on measures of academic achievement revealed no significant main effect for group $F(1,103) = 1.915, p = 0.169$, or time $F(3,192) = 0.573, p = 0.633$, and no significant interaction effect for group x time $F(3,193) = 0.498, p = 0.684$ on the WJ-R Letter Word subtest.

Similarly, on the WJ-R Dictation subtest no significant main effect for group $F(1,99) = 2.452, p = 0.121$, or time $F(3,188) = 0.572, p = 0.634$, and no significant interaction effect for group x time $F(3,188) = 0.498, p = 0.684$ was noted.

On the WJ-R Calculation subtest, no significant main effect for group $F(1,79) = 0.018, p = 0.895$, or time $F(3,115) = 1.002, p = 0.395$ was noted. Additionally, no significant interaction effect for group x time $F(3,115) = 0.738, p = 0.531$ was observed on this dependent measure.

No significant main effect for group $F(1,97) = 0.829, p = 0.365$, or time $F(3,167) = 2.900, p = 0.037$, and no significant interaction effect for group x time $F(3,167) = 1.148, p = 0.331$ was observed on the WJ-R Applied Problems subtest.

The analysis of performance on the BASC-PRF Behavioral Symptoms Index yielded no significant main effect for group $F(1,88) = 0.384, p = 0.537$, or time $F(3,142) = 1.240, p = 0.298$, and no significant interaction effect for group x time $F(3,142) = 0.975, p = 0.406$.

On the BASC-PRF Adaptive Skills composite, no significant main effect for group $F(1,87) = 3.739, p = 0.056$, or time $F(3,148) = 0.634, p = 0.594$ was noted. Additionally, no significant interaction effect for group x time $F(3,148) = 0.389, p = 0.761$ was observed.

On the BASC-PRF Internalizing Problems composite, no significant main effect was noted for time $F(3,148) = 3.641, p = 0.014$, or group $F(1,90) = 1.658, p = 0.201$. Additionally, no significant interaction effect for group x time $F(3,148) = 0.510, p = 0.676$ was observed.

Similarly, no significant main effect for group $F(1,92) = 0.267, p = 0.606$, or time $F(3,149) = 0.510, p = 0.676$ was noted on the BASC-PRF Externalizing Problems composite. Additionally, no significant interaction effect for group x time $F(3,149) = 1.322, p = 0.269$ was observed on this composite.

Analysis of performance on the BASC-SRP yielded no significant main effect for group $F(1,49) = 2.451, p = 0.124$, or time $F(3,82) = 1.475, p = 0.227$ on the Emotional Symptoms Index, and no significant interaction effect for group x time $F(3,83) = 0.984, p = 0.404$.

On the BASC-SRP Personal Adjustment composite, no significant main effect for group $F(1,47) = 1.050, p = 0.311$, or time $F(3,79) = 1.024, p = 0.387$ was noted. Additionally, no significant interaction effect for group x time $F(3,79) = 0.631, p = 0.597$ was observed.

On the BASC-SRP Clinical Maladjustment composite, no significant main effect for group $F(1,50) = 3.367, p = 0.072$, or time $F(3,75) = 0.985, p = 0.405$ was noted, nor was a significant interaction effect for group x time $F(3,75) = 0.595, p = 0.620$ observed.

Similarly, no significant main effect for group $F(1,42) = 0.533, p = 0.468$, or time $F(3,73) = 0.134, p = 0.939$ was noted on the School Maladjustment composite. Additionally, no significant interaction effect for group x time $F(3,74) = 0.655, p = 0.582$ was observed on this composite.

CHAPTER 5

DISCUSSION

The purpose of this study was to examine the performance of children and adolescents with ALL, treated with one of two dosage levels of methotrexate, on various measures of cognitive, academic, and social-emotional/behavioral functioning. Specifically, evidence of changes in performance over time—from initial data collected within the first month after diagnosis through data collected approximately 3 years, 1 month after diagnosis—were of direct interest, as such changes are likely indicative of the late effects of pediatric ALL and its treatment with either $1\text{g}/\text{m}^2$ or $2\text{g}/\text{m}^2$ of methotrexate. The results of this study suggest that pediatric ALL and its treatment with chemotherapy alone does not in and of itself have a statistically significant impact on performance on measures of cognitive, academic, and social-emotional/behavioral functioning.

Findings regarding the differences in performance on measures of cognitive functioning for participants with ALL did not reveal any significant effects of methotrexate dose or time since diagnosis, nor were any significant results yielded through the analyses of the interaction of methotrexate dose and time since diagnosis. These findings are consistent with a number of recent investigations, which have indicated that language skills (MacLean et al., 1995; Précourt et al., 2002; Stehbens et al., 1994) and attention skills (Anderson et al., 2006; Lockwood et al., 1999; Schatz et al., 2004) are relatively preserved in the face of ALL and its treatment with chemotherapy only. However, the current findings fail to support those of several other investigations,

which demonstrated statistically significant declines in global intellectual function (Brown et al., 1996; Brown et al., 1999; Montour-Proulx et al., 2005) in children and adolescents with ALL who were treated only with chemotherapy.

Analyses exploring the differences in performance on measures of academic achievement for participants with ALL also revealed non-significant effects of methotrexate dose, time since diagnosis, and the interaction of these two variables. These current findings in the area of academic achievement similarly contrasted other recent literature that reported statistically significant changes in academic performance (i.e., math, reading, and spelling) over time in pediatric patients with ALL treated only with chemotherapy (Andrews Espy et al., 2001; Brown et al., 1999).

Furthermore, the analyses exploring differences in parent and participant ratings on measures of social-emotional/behavioral functioning did reveal one significant difference due to the main effect of methotrexate dose. In this regard, participants with ALL who were treated with 1g/m^2 of methotrexate were rated more poorly on parent report measures of adaptive skills than were those participants with ALL who were treated with 2g/m^2 of methotrexate. However, the mean score on this measure for each treatment group was within 1 *SD* of the test mean and therefore neither group's average score was in the range of clinical concern. These results lend support to the findings of Shelby et al. (1998), which described significantly worse parent reports of adaptive functioning in pediatric populations with ALL.

The absence of other statistically significant differences in performance means independent of methotrexate dose is important in demonstrating that the specific

variations in methotrexate dosage level evaluated in this study did not appear to differentially impact performance on the vast majority of dependent measures. The general absence of significant results on measures of parent-reported measures of social-emotional/behavioral functioning (with the exception of adaptive skills) was particularly surprising as several recent investigations have reported statistically significant findings with regard to the presence of internalizing symptoms (e.g., Earle & Eiser, 2007; Portteus et al., 2006; Shelby et al., 1998) and externalizing symptoms (e.g., Noll et al., 1997; Shelby et al., 1998) in pediatric populations with ALL treated only with chemotherapy.

Given the existing empirical findings in support of younger age at diagnosis being a risk factor for cognitive late effects due to pediatric ALL and its treatment (Langer et al., 2002; Précourt et al., 2002), but a protective factor against social-emotional/behavioral late effects (e.g., Earle & Eiser, 2007; Shelby et al., 1998), age at diagnosis was considered in the analyses of performance of participants with ALL. In this regard, participants who were younger than 5 years of age at diagnosis performed significantly worse on a measure of visual-spatial attention and working memory than did those who were 5 years of age and older at diagnosis. The group mean score for those participants younger than 5 years of age at diagnosis exceeded $.5 SD$ below the test mean, whereas the group mean score of those participants who were 5 years of age or older at diagnosis was within $.5 SD$ of the test mean. These findings lend indirect support to those of Langer et al. (2002) and Précourt et al. (2002), both of which reported age-related effects of ALL and its treatment on nonverbal tasks. In another analysis, participants who were younger than 5 years of age at diagnosis performed significantly higher, on average,

on an academic achievement measure of spelling and written language abilities than did those participants who were 5 years of age or older at diagnosis, although neither group's mean score exceeded 1 *SD* below the test mean. This significant main effect for age on measures of academic achievement was not previously observed in any of the recent literature reviewed and thus yields new findings that will require replication. No other analyses of differences related to age at diagnosis were significant. Additionally, no analyses evaluating the interaction effect for age at diagnosis and time since diagnosis were significant. Overall, this indicates that pediatric ALL its treatment was not shown to have more significant effect on longitudinal changes in cognitive, academic, and social-emotional/behavioral function when diagnosed prior to 5 years of age or when diagnosed at 5 years of age or older.

The performance of participants with ALL on measures of cognitive, academic, and social-emotional/behavioral functioning was also compared against that of non-ALL sibling participants to further delineate whether any identified changes in performance were outside the realm of those expected to occur over time in a sample of individuals not affected by ALL and its treatment. In this regard, no significant differences emerged between groups or when the entire sample was considered with regard the effect of time. Additionally, no significant findings were revealed for the interaction of group membership and time, indicating that fluctuations in the performance of participants with ALL over the 3 year time period were not significantly different from those observed in the non-ALL sibling group over the same time period. Overall, this lack of significant findings is important because it indicates that individuals treated for pediatric ALL, with

either 1g/m² or 2g/m² of IVMTX, may not demonstrate cognitive, academic, or social-emotional/behavioral late effects within the first 3 years after diagnosis.

When evaluating these findings in light of recent empirical research, the lack of significant differences between pediatric patients with ALL and a group of non-ALL siblings lends support to the findings of Schatz et al. (2000) who reported no differences on measures of intellectual function, memory, reading, or math when comparing participants with ALL treated with chemotherapy and healthy individuals. However, the current results are in contrast to the findings of several other investigations that lend support to the impact of ALL and its treatment with chemotherapy only on measures of intellectual performance when compared with healthy individuals (Hill et al., 1997; Langer et al., 2002; Lofstad et al., 2008; Précourt et al., 2002; Raymond-Speden et al. 2000; Reinfjell et al., 2007). Although these aforementioned investigations reported statistically significant results with regard to between group differences on measures intellectual performance, several also indicated that performance means for the compared groups all remained within the average range of intellectual function (Brown et al., 1998; Précourt et al., 2002; Reinfjell et al., 2007), a result that was also observed in the current investigation. The current results also fail to support several other recent empirical investigations of cognitive functioning in pediatric patients with ALL. Specifically, memory function was previously demonstrated to be worse in individuals with ALL treated only with chemotherapy when compared with healthy peers (Hill et al., 1997; Kleinman & Waber, 1994; Montour-Proulx et al., 2005, Précourt et al., 2002); the current study failed to find similar group differences. Furthermore, Raymond-Speden et al.

(2000) and Brown et al. (1998) demonstrated a significant impact of ALL and its treatment on visual-spatial skills when ALL participants were compared to healthy peers; this finding was also not supported in the current investigation.

Overall, these findings suggest that the treatment of pediatric ALL with $1\text{g}/\text{m}^2$ or $2\text{g}/\text{m}^2$ of IVMTX does not significantly impact the incidence of late effects with regard to cognitive, academic, and social-emotional/behavioral functioning within the first 3 years post-diagnosis, with the exception of adaptive skills. Younger age at diagnosis may, however, protect against declines in performance on measures of spelling and written expression skills due to ALL and its treatment. In contrast, younger age at diagnosis may serve as a risk factor for below average performance on measures of visual-spatial attention and working memory due to ALL and its treatment.

Although reviewing clinically significant (i.e., values $\geq 1\text{ SD}$) between and within group differences of participants with ALL was not the purpose of this study, the data were available and so these were examined. This information can be useful to psychologists and educators working with survivors of pediatric ALL in order to determine their need for intervention services and potential eligibility for special education. In this regard, analyses comparing participants with ALL treated with $1\text{g}/\text{m}^2$ to those treated with $2\text{g}/\text{m}^2$ of methotrexate revealed clinically meaningful findings on measures of math calculation skills, behavioral regulation (an executive function), and internalizing symptoms. Specifically, participants younger than 5 years of age at diagnosis showed large declines in performance on a measure of math calculation skills when comparing the Year 1 follow-up and Year 3 follow-up assessments, with group

means declining from the high average range to the average range. Participants treated with $1\text{g}/\text{m}^2$ of methotrexate were found to be significantly worse in their abilities to initiate, shift, and inhibit behavioral response patterns and to control their emotional responses than were those participants treated with $2\text{g}/\text{m}^2$ of methotrexate at the Year 3 follow-up assessment. In contrast to this pattern of group differences, however, those participants treated with $1\text{g}/\text{m}^2$ of methotrexate demonstrated clinically meaningful declines in internalizing symptoms between the initial assessment and the Year 3 follow-up assessment.

In conclusion, this study lends support to the existing literature by investigating the specific impact of two contemporary treatment protocols used for pediatric ALL on cognitive, academic, and social-emotional/behavioral functioning with a strong methodology. Specifically, previous findings regarding the deleterious effects of ALL and its treatment on adaptive skills (Shelby et al., 1998), and of younger age at diagnosis on nonverbal tasks (Langer et al., 2002; Précourt et al., 2002) were largely supported by the current study. Furthermore, previous investigations that reported the relative preservation of language skills (MacLean et al., 1995; Précourt et al., 2002; Stehbens et al., 1994) and attention skills (Anderson et al., 2006; Lockwood et al., 1995; Schatz et al., 2004) in pediatric patients treated for ALL were also largely supported by the current findings. Perhaps the most surprising findings were related to the analyses comparing participants with ALL to a group of non-ALL siblings, which overall failed to support much of the preexisting literature by observing non-significant group differences on measures of intellectual function (Hill et al., 1997; Langer et al., 2002; Précourt et al.,

2002; Raymond-Speden et al. 2000; Reinfjell et al., 2007), memory (Hill et al., 1997; Kleinman & Waber, 1994; Montour-Proulx et al., 2005, Précourt et al., 2002), and visual-spatial skills (Brown, et al., 1998; Raymond-Speden et al., 2000).

The fact that the sample was homogeneous in terms of diagnosis, comprised of participants randomly assigned to treatment group, and further incorporated a non-ALL sibling comparison group lends methodological integrity to the existing literature base. Furthermore, the utilization of a longitudinal design further supports the meaningfulness of the findings to professionals in the fields of psychology and education, whose aim is to understand the late effects of ALL and its treatment in pediatric populations and provide appropriate intervention services designed to address these cognitive, academic, and social-emotional changes that occur.

Limitations

There were some clear limitations to this study. Specifically, the relatively small sample size in each ALL treatment group points to the need for conducting a similar study with a larger sample size to confirm the current findings. In addition, this study analyzed performance on a large number of dependent variables and incorporated conservative significance levels to control for the increased probability of spurious findings due to a Type I error. In reviewing the data after the fact, several analyses were observed to have alpha levels less than .05 and thus the findings in the current study may be the result of a Type II error due to the conservative setting of significance levels.

The lack of significant changes in performance over time in the analyses comparing only participants with ALL may be related to participant attrition.

Specifically, it is not known what differences in functioning may exist between those participants lost through attrition and those remaining in the study through the follow-up assessment periods; it is entirely possible that those participants remaining in the study had higher average performance on the dependent measures which obscured any real late effects that may be apparent in survivors of pediatric ALL.

One major limitation to exploration of the age at diagnosis variable, included that several dependent measures were not normed on children less than 5 years of age, a factor which restricted administration of those measures to younger children at the initial assessment period. Given that this “baseline” (i.e., pretreatment) data point was missing, these children were not included in analyses of performance on specific dependent measures, which reduced sample size.

There are additional limitations with regard to the lack of significant findings in the analyses comparing participants with ALL to a group of healthy siblings. Specifically, it is unknown whether those siblings who participated in this study were indirectly impacted by having a sibling with a chronic illness.

Additionally, the moderate to high test-retest reliability coefficients for the dependent measures used in this study warrant consideration in a longitudinal design. Small, albeit statistically significant, changes in performance may not be clinically meaningful when considered with this particular psychometric property in mind (i.e., participants could not be expected to receive the exact same score on a measure over the course of repeated administrations). Furthermore, consideration of the *standard error of measurement* associated with each subtest and composite score is useful for

discriminating between mere statistical significance and those instances where statistically significant differences also have clinical utility.

Directions for Future Research

Future research will benefit from continued exploration, through longitudinal design, of the impact of ALL and its treatment with only chemotherapy. Larger sample sizes, consistent use of standardized assessment measures, and expansion of the follow-up assessment periods to 5 or even 10 years post-diagnosis would be beneficial. Future research should consider including a comparison group of non-ALL participants, unrelated to those participants with ALL, in addition to the non-ALL sibling comparison group. Future research may also consider alternative analysis procedures, such as repeated measures MANOVA, which would allow for significance testing at a more liberal value. This goal could be similarly achieved through reduction of the number of dependent variables examined by honing in on one or two specific domains of functioning. Another alternative might include use of a growth curve analysis procedure. Specific reasons for participant attrition are not known, and given the impossibility of collecting data from those participants lost to attrition, it is difficult to be certain that the lack of significant findings is not an artifact of specific innate qualities of those participants remaining throughout the study's completion—for instance, higher premorbid intellectual functioning. Future attempts to examine group differences between those participant remaining in the study and those lost to attrition are suggested. Another way in which future studies could correct for this would be to use different statistical analysis procedures that incorporate list-wise deletion of those participants lost through

attrition before the study's completion; a procedure such as this, however, would substantially limit the sample size included in each analysis. Additionally, with regard to methodology, exploration of academic achievement in pediatric survivors of ALL should consider collecting school-based data (e.g., teacher rating scales, grade reports, reports of special education referrals and placement, receipt of pre-referral interventions, etc) as this information could be useful with regard to the functional impact of ALL and its treatment on pediatric patients performance in academic environments, which would support the generalization of findings. As our understanding of the specific impact of pediatric ALL and its treatment on the cognitive, academic, and social-emotional/behavioral functioning increases, psychologists and educators working with these individuals will be better equipped to implement preventive techniques to counteract declines in functioning.

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