Declines Noted in Cognitive Processes and Association With Achievement Among Children With Leukemia

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This research was funded by a grant (R01NR010889, with Ida M. Moore as principal investigator) from the National Institute of Nursing Research at the National Institutes of Health.

Insel, Hockenberry, Harris, and Moore contributed to the conceptualization and design. Insel, Harris, Koerner, Adkins, Taylor, Gundy, and Moore completed the data collection. Insel, Koerner, Lu, and Moore provided statistical support. Insel, Hockenberry, Koerner, Adkins, and Moore provided the analysis. Insel, Hockenberry, Harris, Koerner, Adkins, Taylor, and Moore contributed to the manuscript preparation.

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Submitted August 2016. Accepted for publication November 30, 2016.

Keywords: longitudinal study; child development; neuropsychology; clinical; cognitive; academic outcomes

ONF, 44(4), 503–511.

doi: 10.1188/17.ONF.503-511

Purpose/Objectives: To assess change in specific cognitive processes during treatment with chemotherapy only among children with acute lymphoblastic leukemia (ALL).

Design: A prospective, repeated measures design.

Setting: Pediatric oncology treatment centers at Banner–University Medical Center Tucson/Banner Children's–Diamond Medical Center (University of Arizona) and Texas Children's Cancer and Hematology centers (Baylor College of Medicine) in Houston.

Sample: 71 children with ALL, with a mean age of 6.18 years at the time of diagnosis.

Methods: Using mixed-effects latent growth curve modeling with time since diagnosis as a fixed effect, age-adjusted standardized measures of working memory, processing speed, executive function, and attention were obtained and repeated about one and two years later. A subsample was tested for academic achievement at the end of treatment.

Main Research Variables: Verbal working memory, visual spatial memory, processing speed, academic achievement, age, and gender.

Findings: A significant main effect was observed for age at diagnosis on decline in verbal working memory during treatment. Planned contrasts revealed greater decline among children who were diagnosed when aged younger than five years compared to those diagnosed when aged five years or older. Decline in verbal working memory and achievement in letter-word identification and calculation skills were associated, and decline in spatial memory was associated with calculation. A main effect of gender was observed on processing speed, with female patients showing greater decline than male patients.

Conclusions: Findings from this study may guide the timing of interventions that could improve school achievement among survivors.

Implications for Nursing: Children undergoing treatment for ALL may experience issues with verbal working memory and increased difficulty in school. Nurses are in a position to refer parents and children to school resources for additional academic support.

Neurocognitive sequelae associated with treatment for childhood acute-lymphoblastic leukemia (ALL) are well documented when treatment includes cranial radiation (Copeland et al., 1985; Edelmann et al., 2014; Fletcher & Copeland, 1988; Krull et al., 2013). Use of intrathecal and systemic chemotherapy has now largely replaced cranial radiation for presymptomatic treatment of the central nervous system (Richards, Pui, & Gayon, 2013) with evidence for improvement in neurocognitive outcomes. In a systematic review of literature from 1997 to July 2008 that reported outcomes among survivors of childhood ALL treated with chemotherapy only, 8 of 10 studies included measures of general intelligence and found no impairment in total intelligence quotient (IQ) (Buizer, de Sonneville, & Veerman, 2009). However, among the eight studies examined by Buizer et al. (2009) that featured measures

of academic achievement, four noted problems in this realm, suggesting that chemotherapy may have more subtle effects on cognitive processes that are important for success in school (Kingma et al., 2002; Schuitema et al., 2013).

The childhood leukemia literature has evolved beyond just global IQ to include a more detailed investigation of neurocognitive effects. Even with newer ALL treatment protocols, lower performance on measures of attention (Buizer, de Sonneville, van den Heuvel-Eibrink, & Veerman, 2005; Conklin et al., 2012; Jacola et al., 2016; Jansen et al., 2006) and processing speed (Buizer et al., 2005; Mennes et al., 2005) have been noted. In addition, chemotherapy is consistently associated with lower-than-expected performance among survivors 120 weeks postconsolidation on attention, reading and math achievement, motor processing speed (Edelmann et al., 2014; Jacola et al., 2016), and working memory (Ashford et al., 2010) compared to norm reference groups (Cheung & Krull, 2015). Age appears to moderate the effect of treatment on cognition, with younger children performing more poorly and girls being more affected than boys (Campbell et al., 2007; Ciesielski, Lesnik, Benzel, Hart, & Sanders, 1999; Jain, Brouwers, Okcu, Cirino, & Krull, 2009).

Less well described are the potential effects of chemotherapy on working memory during treatment. Working memory involves temporary holding and manipulation of information and, consequently, requires attention and capacity (Baddeley, 2012; Gathercole, Pickering, Knight, & Stegmann, 2004). Working memory is needed for complex cognitive tasks (Baddeley, 1992, 2000) and is implicated in academic achievement (e.g., language comprehension, problem solving, mental arithmetic) (Engle, Tuholski, Laughlin, & Conway, 1999), as well as with literacy and mathematics among school-aged children and achievement in science and mathematics among older children (Bull & Lee, 2014; Gathercole, Pickering, Knight, & Stegmann, 2004). Working memory is present even in young children, with increases in the capacity of working memory occurring through the early and middle-school years and adolescence (Gathercole, Pickering, Ambridge, & Wearing, 2004). Early identification of declines in working memory during treatment could improve understanding about when deficits occur, as well as the association of these deficits with academic achievement, and trigger early referral for school resources.

The purpose of this study was to examine rate of change during treatment in working memory, processing speed, executive function, and attention among children diagnosed with ALL and receiving chemotherapy. The current authors hypothesized that a decline would occur from the initial measure relative to age-adjusted norm reference groups during treatment in these particular cognitive processes. The authors also examined age at the time of diagnosis, risk group, and gender. Of particular interest was decline in working memory as a possible explanation for lower school achievement.

Methods

This study was a prospective, repeated measures design examining intra-individual change over time.

Participants

Seventy-one children were sequentially enrolled in the study during a four-year period. All were diagnosed with ALL and received treatment according to protocols from the Children's Oncology Group (COG): AALL0331 (n = 34, standard risk), AALL0031 (n = 1, very high risk), AALL0622 (n = 1, high risk), AALL0232 (n = 15, 2 standard risk and 13 high risk), AALL0932 (n = 11, 2 low risk, 8 standard risk, and 1 high risk), AALL1131 (n = 6, 5 high risk and 1 very high risk), and AALL0434 (n = 3, 2 low risk and 1 standard risk). Children were assigned to treatment risk group twice: at diagnosis, according to National Cancer Institute/Rome Criteria (Smith et al., 1996), and postinduction, according to the specific COG protocol followed. The second risk assignment used in this analysis included considerations of genetic markers and response to induction therapy. Treatment varied in length from about 2–3.5 years.

Specific medications were determined by the therapy protocol; that is, not all children received all medications. None of the children in this analysis were treated with cranial irradiation. Children were aged 2–15 years when diagnosed and 3–17 years when they participated in the cognitive testing. The measures in the cognitive battery are available in English, and participants had to be sufficiently fluent in English to complete the measures without an interpreter (although non-English–speaking parents could give consent in their dominant language). Exclusion criteria included diagnoses of neurologic disorders or neurodevelopmental disabilities (e.g., seizures, Down syndrome).

Procedures

Participants were recruited from two pediatric oncology treatment centers (Banner–University Medical Center Tucson/Banner Children's–Diamond Medical Center [University of Arizona] and Texas Children's Cancer and Hematology centers [Baylor College of Medicine] in Houston) with approval from the University of Arizona Human Subjects Protection Program and the Baylor University Committee for Protection of Human Subjects in Research. Children assented to study involvement, whereas parents provided formal informed consent as soon as possible following diagnosis. Children who agreed to participate were tested

using a cognitive battery as soon as they could be scheduled following initiation of treatment and then annually, as permitted by scheduling.

Measures

A demographic form was used to gather information on the child's age and gender, maternal and paternal achieved education, race and ethnicity, and treatment risk. Cognitive measures were used to assess working memory, processing speed, executive function, and attention.

Working memory was assessed with the Wide Range Assessment of Memory and Learning–Second Edition (WRAML-2) (Sheslow & Adams, 2003). Specifically, the subtests used were Finger Windows and Number/Letter. Finger Windows is a visual-spatial memory task (the child must replicate a pattern created by the administrator, who inserts the blunt end of a pencil into predetermined holes of a plastic template), whereas Number/Letter is a verbal working memory task. The Number/Letter subtest requires that the child listen to the administrator read a series of numbers and letters presented in no particular order. The child is then required to repeat the numbers in numerical order and the letters in alphabetical order. As the items are completed correctly, the amount of numbers and letters increases. Each subtest and the composite were converted to age-adjusted standard scores with a mean of 100 and a standard deviation of 15 using national norms. Testing with the WRAML-2 begins at age five years (see Table 1).

Processing speed was assessed with the Woodcock-Johnson III (WJ III) Tests of Cognitive Abilities (Woodcock, McGrew, & Mather, 2001) and specifically with two subtests: Visual Matching and Decision Speed. Both are timed tests that require children to find matching items in rows. Visual Matching comes in two versions: one with numbers for school-age children and one with shapes for younger children. Decision Speed consists of rows of pictures with a pair of similar items in each row. The child is asked to select the two pictures that are similar. Standard scores were obtained for each measure and for the composite of processing speed based on a mean of 100 and a standard deviation of 15. The WJ III tests were completed by participants of all ages.

Executive function was measured using the Animal Sorting, Auditory Attention and Response Set, Clocks, Design Fluency, Inhibition, and Statue subtests on the NEPSY-II, which stands for a Developmental NEuroPSYchological Assessment (Korkman, Kirk, & Kemp, 2007). An advantage of the NEPSY-II is the opportunity to obtain age-appropriate indicators of executive function. The Animal Sorting subtest evaluates the child's ability to make unique sets of cards by finding similarities and also to create new sets. Auditory Attention assesses attention vigilance and requires that the child listen to a series of words and respond when a target word is heard, whereas the Response Set requires that the child listen to a new set of words and respond in a different manner to target words, which tests the child's ability to shift to a new task and inhibit automatic responses. For the Clocks subtest, children are directed to draw analog clocks to assess planning and organization. The Design Fluency subtest gives children one minute to create as many unique designs as possible on a grid with five dots. The Inhibition subtest is composed of three parts: naming, inhibition, and switching. Each section involves naming shapes,

TABLE 1. Cognitive Abilities Assessed

Variable	Description	Measure
Achievement	Grade-level standard achievement in letter-word identification and calculation	Letter Word Identification and Calculation subtests from Woodcock-Johnson III Tests of Achievement
Attention	Assessment of sustained and focused attention	Conners' Continuous Performance Test II and Conners' Kiddie Continuous Performance Test
Executive function	Control processes that regulate thoughts and behavior through inhibiting, updating, and monitoring	Animal Sorting, Auditory Attention and Response Set, Clocks, Design Fluency, Inhibition, and Statue subtests from NEPSY-II
Processing speed	Automatically and fluently perform relatively easy tasks; measured with timed tests	Visual Matching and Decision Speed subtests from Woodcock-Johnson III Tests of Cognitive Abilities
Working memory (verbal)	Temporary holding and manipulation of verbal and auditory information; involves attention and capacity	Number/Letter subtest from Wide Range Assessment of Memory and Learning–Second Edition
Working memory (visual-spatial)	Temporary holding and manipulation of visual-spatial information; involves attention and capacity	Finger Windows subtest from Wide Range Assessment of Memory and Learning–Second Edition

but the rules change for inhibition and switching. Children must inhibit automatic responses to score well on the subtest. Finally, the Statue subtest measures a child's ability to ignore distractions and remain focused and still. A composite executive function score was calculated by averaging the subtest scores. The specific battery of subtests administered was based on the child's age. Children aged 3–4 years completed only the Statue subtest; children aged 5–6 years completed the Auditory Attention, Design Fluency, Inhibition, and Statue subtests; children aged 7–12 years completed all of the subtests except for the Statue subtest; and children aged 13–17 years completed all of the subtests except for the Design Fluency and Statue subtests.

Attention was assessed with the Conners' Continuous Performance Test II (CPT II) (Conners, 2004) and the Conners' Kiddie Continuous Performance Test (K-CPT) (Conners, 2006). For the CPT II, children are shown one letter at a time on a blank screen and instructed to press the space bar every time a letter is seen, except for when an "x" appears. The K-CPT is similar, except that simple pictures are used rather than letters, and a soccer ball is used in place of the "x." An overall CPT score was calculated by averaging the t scores for omissions, commissions, and perseverations. With more omissions, the child has less opportunity for commissions; however, in the setting of more omissions and then commissions on the attempted items, the total errors are meaningful. The K-CPT is appropriate for children aged 4–5 years, whereas the CPT II is used for children aged 6 years or older.

Achievement was assessed with the WJ III Tests of Achievement (Woodcock et al., 2001) using the Letter Word Identification and Calculation subtests. The Letter Word Identification subtest measures word skills by requiring the child to identify letters and then words. The Calculation subtest assesses the child's ability to perform computations. Initially, the child must write single numbers. The remaining items require addition, subtraction, multiplication, division, and combinations of these operations. Items for older children and for those of high ability assess geometric, trigonometric, logarithmic, and calculus operations. Both subtests are appropriate for children aged 5–19 years.

Statistical Analyses

Descriptive statistics were computed for demographic characteristics. Performance on neurocognitive measures was reported as age-adjusted standard scores, which account for the expected improvement in cognitive ability during development; consequently, change in age-adjusted standard scores reflects change in ability. Analysis of the longitudinal data used growth curve modeling (also known as linear mixed-effects models with random coefficients), and the initial value and growth rate for each participant was composed of fixed (population) and subject-specific random effects, enabling the estimate of the rate of change over time. Time since diagnosis was a fixed effect, allowing for variation in data collection intervals among participants. Data were collected during three time periods: as soon as possible after the start of treatment and at one and two years later.

Academic abilities were assessed with the WJ III Letter Word Identification and Calculation subtests in a subset of children who were available for testing at the completion of ALL treatment. The intent was to examine correlations between the slopes for the cognitive tests that showed significant declines relative to the age-adjusted norm reference group and measures of achievement.

Main effects of age at the time of diagnosis, along with gender and leukemia risk level, were obtained. Just four children were categorized as low risk, so, for the purposes of comparing risk, this group was combined with the standard-risk group (N = 49). In addition, the very high-risk group contained just two children, who were then combined with the high-risk group (N = 22). When the main effects were significant, planned comparisons examined rate of change in each cognitive assessment between the youngest age group and the pooled three oldest age groups and between genders. The planned comparisons were based on the literature indicating that younger age at diagnosis and female gender predict worse cognitive outcomes (von der Weid et al., 2003).

Missing data occurred because children occasionally declined to complete a measure. The current authors assume the "missingness" mechanism is missing at random (MAR) (Mazza, Enders, & Ruehlman, 2015; Muthen, 1991; Nesselroade, 1991). Latent growth curve modeling uses full information maximum likelihood for inference and is robust to MAR data.

Results

Seventy-one children diagnosed with ALL were enrolled and assented to participation, and their parents or legal guardians consented to their participation. Thirty-nine children were female and 32 were male, with a mean age of 6.18 years (SD = 3.07) at the time of diagnosis. At the time of diagnosis, 32 children were aged 3 years to less than 5 years, 16 were aged 5 years to less than 7 years, 9 children were aged 7 years to less than 9 years, and 14 children were aged 9 years or older. Specific characteristics of the sample are provided in Table 2.

No significant differences were noted in maternal education by age group at time of diagnosis (F = 1.33, p = 0.27) or gender (t= –1.08, p = 0.28) or in paternal education by age group at time of diagnosis (F =

0.285, p = 0.836) or gender (t = 0.341, p = 0.734). No main effects were found for risk group on any of the cognitive measures over time.

In the model that included age at diagnosis, gender, and risk, no differences were observed in rate of change for Finger Windows, Decision Speed, NEPSY-II, or CPT II. Main effects of age at diagnosis were noted on the Number/Letter subtest ($F = 2.98$, $p < 0.05$) and in the composite WRAML-2 ($F = 3.52$, $p < 0.05$). Examination of contrasts revealed that the Number/Letter subtest results and WRAML2 growth rates for participants diagnosed when aged younger than five years were significantly different than for participants who were aged at least five years at diagnosis. Children who were aged younger than five years at the time of diagnosis showed greater negative slopes in Number/Letter subtest results over the three measurement occasions ($t = 2.91$, $p < 0.01$). Those who were aged younger than five years at the time of diagnosis also differed significantly on the WRAML2 ($t = -3.21$, $p < 0.01$) compared to those who were aged five years or older at diagnosis. The Number/Letter subtest of the WRAML2 shows a negative slope, indicating decline during the measurement occasions; however, when Number/Letter is combined with Finger Windows, the slope is positive. A main effect of gender was observed on visual matching, with female participants showing greater decline ($F = 4.14$, $p < 0.05$).

Correlations among the WJ III subtests of Letter Word Identification, Calculation, and Visual Matching and the WRAML-2 composite score and the individual components of Number/Letter and Finger Windows were obtained on a subgroup of 43 children for Visual Matching and 29 children for the WRAML-2. The slope representing change over time in verbal working memory was significantly associated with the Letter Word Identification and Calculation subtests ($r = 0.552$, $p < 0.01$ and $r = 0.434$, $p < 0.05$, respectively). The slope representing change over time in the Finger Window subtest, as a measure of visual-spatial memory, was significantly correlated with the Calculation subtest ($r = 0.371$, $p < 0.05$) (see Table 3).

Discussion

Findings indicate a main effect of age on verbal working memory (Number/Letter subtest),

TABLE 2. Participant Characteristics by Cognitive Ability

Characteristic	Overall (N = 71)		Working Memory (N = 60)		Processing Speed (N = 66)		Visual Matching (N = 67)		Decision Speed (N = 65)		Executive Function (N = 71)		Attention (N = 60)	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Age at diagnosis (years)	6.18	3.07	6.71	3.04	6.33	3.12	6.3	3.11	6.41	3.1	6.18	3.07	6.68	3.06
Maternal education (years)[a]	13.31	2.36	13.38	2.34	13.43	2.35	13.44	2.34	13.45	2.37	13.31	2.36	13.44	2.42
Paternal education (years)[a]	12.94	2.72	13	2.85	13	2.72	13.05	2.73	12.98	2.77	12.94	2.72	12.95	2.83

Characteristic	n	n	n	n	n	n	n
Gender							
Female	39	33	37	37	36	39	34
Male	32	27	29	30	29	32	26
Race/ethnicity							
Caucasian	28	23	26	26	26	28	22
Hispanic	36	32	34	35	33	36	32
African American	3	2	3	3	3	3	3
Native American	2	1	1	1	1	2	1
Other	2	2	2	2	2	2	2
Treatment risk							
Low	4	3	3	4	3	4	3
Standard	45	39	42	42	42	45	39
High	20	17	19	19	18	20	17
Very high	2	1	2	2	2	2	1

[a] Not all participants provided parental education information (67 provided years of maternal education, and 66 provided years of paternal education).

in which children diagnosed with ALL and treated with chemotherapy show decline compared to age-based norm references during the three data collections. Although children diagnosed when aged younger than five years were not assessed for working memory until they were aged five years, they showed greater decline in verbal working memory compared to children who were diagnosed when aged five years or older. To the current authors' knowledge, intra-individual change in cognitive processes during treatment has not previously been assessed. Although the negative slope was steepest for the youngest participants, children aged older than five years at diagnosis also had negative slopes in verbal working memory. Verbal working memory performance decreased across all age groups during treatment. These findings converge with prior cross-sectional studies involving survivors of childhood ALL, indicating that age at diagnosis is a risk factor for poorer outcomes even among children treated with chemotherapy only (Ashford et al., 2010; von der Weid et al., 2003). This finding provides new information regarding when decline can be observed and, as a result, has implications for the timing of interventions to prevent or minimize decline.

The WRAML-2 composite score is considered to be a measure of working memory. It is comprised of the Finger Windows subtest, a measure of visual-spatial memory, and the Number/Letter subtest, a measure of verbal working memory. The WRAML-2 was also significant in planned contrasts using aged younger than five years and aged five years or older. However, the slopes were positive. Although not significant, the results of Finger Windows improved during the three measurement occasions. Visual-spatial memory may have improved because of practice. In a study examining the effect of practice on Finger Windows subtest results, a significant study years by age (representing the number of exposures to the test the child had) subgroups interaction was found, indicating differential practice effects for different age subgroups (Slade et al., 2008). Children in this study were aged 8–11 years, and younger children benefited more from practice. Improvements on retest can also be attributable to the child feeling better and performing higher on the measure. To counter this argument, improvements in verbal working memory, as assessed with the Number/Letter subtest, were not seen; in fact, decline was observed. Data collection for the Finger Windows and Number/Letter subtests occurred during the same testing session. Finding that children with ALL treated with chemotherapy performed better on the visual-spatial memory measure of the WRAML-2 compared to the verbal working memory measure of the WRAML-2 suggests that these measures differ. That is, visual-spatial memory, as measured with the Finger Windows subtest, is not a working memory measure, but it is part of the working memory composite. Potential exists for ambiguity in interpreting a composite measure. The WRAML-2 composite measure of working memory is constructed from tasks that perform differently from one another. Reliance on the composite WRAML-2 would suggest that working memory is not adversely affected in children with ALL exposed to chemotherapy. However, a different conclusion emerges when a more thoughtful approach is taken to deciphering components of the WRAML-2. The Number/Letter subtest of the WRAML-2, in which children must hold in their memory and manipulate the order of numbers and letters as the string of numbers and letters increases, is characteristic of working memory tasks and shows decline over time in this sample.

Implications of declines in verbal working memory may signal an increased risk for diminished school achievement and greater difficulty in everyday function. In the current study, declines in verbal working memory during treatment were associated with lower achievement scores in letter word identification and calculation abilities one year later. Others have found working memory performance and phonological awareness to be predictors of learning among young children initially tested in kindergarten and then two years later (Alloway, Alloway, & Wootan, 2014; Alloway, Gathercole, Kirkwood, & Elliott, 2009; Christopher et al., 2012). Working memory is also linked to reading achievement independent of phonological

TABLE 3. Correlation Coefficients for Change Over Time and Achievement

Measure	Letter Word ID	Calculation	VM Slope	WRAML-2 Slope	FW Slope	Number/ Letter Slope
Letter Word ID	–	–	–	–	–	–
Calculation	0.558**	–	–	–	–	–
VM slope	0.076	0.218	–	–	–	–
WRAML-2 slope	0.105	0.359	0.091	–	–	–
FW slope	0.24	0.371*	0.167	0.6**	–	–
Number/Letter slope	0.552**	0.434*	0.181	–0.051	0.026	–

* $p < 0.05$; ** $p < 0.01$
FW—Finger Windows; VM—Visual Matching; WRAML-2—Wide Range Assessment of Memory and Learning–Second Edition

skills (Christopher et al., 2012; Nevo & Breznitz, 2011). Measures of working memory in the current study may also be capturing mental flexibility and inhibition, cognitive processes more often thought of as executive processes in adults, because, among young children, mental flexibility may be less differentiated from working memory and inhibition (St. Clair-Thompson & Gathercole, 2006).

Achievement in calculation was significantly associated with verbal working memory and visual-spatial memory. Survivors of childhood cancer have reported increased difficulty with concentration, working speed, and working memory (Wengenroth et al., 2015). Converging evidence for the associations found in the current study is offered in a nonclinical population of children aged 11–12 years when examining working memory and English and mathematics achievement (Bull & Lee, 2014; St. Clair-Thompson & Gathercole, 2006). Several measures of working memory (listening recall, backward digit span, odd-one-out, spatial span) were associated with achievement in English, whereas the odd-one-out and spatial span measures were associated with achievement in math. In addition, children who have poor working memory may also have difficulty remembering and carrying out instructions, keeping track of school-related tasks, writing while planning text, and performing mental arithmetic. As a result, declining working memory during treatment may affect school achievement.

The expected trajectory of development of working memory in children appears to be adversely affected by chemotherapy. Interventions to address negative sequelae are underway but considered to be underdeveloped (Olson & Sands, 2016). Knowledge of the cognitive processes affected during treatment could inform interventions to prevent or manage changes and decrease the deleterious effects on school achievement and everyday function. In addition, earlier interventions occurring while the child is receiving treatment may alter the negative trajectory of decline in verbal working memory and consequent negative association with academic achievement.

Female gender was associated with more vulnerability compared to male gender. In particular, a downward trajectory was noted in one measure of processing speed. Other studies have suggested differential effects in treatment for female patients compared to male patients (Jain et al., 2009; von der Weid, 2001) but have not always cited differences in processing speed. This could be because of differences in the tests used to measure processing speed. Different cognitive assessments are not necessarily pure measures of specific processes. For example, Jain et al. (2009) identified poorer performance for female patients specific to shifting and sustaining attention. Processing speed is sometimes found to be congruent with measures of sustained attention and may be captured in measures of problem-solving or fine/visual-motor processing. Processing speed and attention may involve overlapping dependent neurosystems because speed is related to attention. Consequently, the evidence may be more consistent than at first glance. However, why female patients appear to be particularly vulnerable to the effects of leukemia treatment is unclear.

The authors did not find decline in executive function or attention in this study. One explanation is that other studies may have used different assessments for these specific processes. For example, working memory has been combined with measures of executive function (Krull et al., 2013). In addition, how attention is measured is sometimes unclear. Indications of the specific subtests used to assess cognitive processes, rather than only global terms (e.g., attention), would improve understanding of the exact processes affected. Commission errors are considered signs of impulsivity and may reflect executive function rather than attention (Fahie & Symons, 2003). In the current study, the authors combined errors of omission, commission, and perseveration as the measure of attention.

Contrary to expectation, risk group was not a predictor of differences in rate of change among the cognitive measures. However, categorization of risk group may have been heterogeneous and overlapping, with additional concern regarding the low number of children in the low-risk and very high–risk groups, which required pooling of these extremes into the standard- and high-risk groups, respectively. A larger sample size may have afforded the ability to find cognitive differences. Characteristics of this sample may have influenced the lack of significant differences found between risk group and cognitive outcomes.

Knowledge Translation

- Children with leukemia, particularly those who are diagnosed when aged younger than five years, may experience a decline in working memory during treatment, which has been associated with lower school achievement.
- Decline in spatial memory during treatment was associated with lower calculation scores.
- Female patients show a decline in processing speed during treatment.

Implications for Nursing

Pediatric oncology nurses are frequently the main point of communication with the child's family and

school. Informing parents and caregivers of the potential impact of treatment on the child's working memory and academic abilities is important because they will be better positioned to advocate for resources to support their child's academic success. Once the child is medically stable and able to return to school, educators need to be aware of the potential impact of ALL treatment on cognitive and academic abilities to provide any necessary accommodations and possible referrals for neuropsychological testing. Pediatric oncology nurses who practice in long-term follow-up and survivorship programs should query parents about cognitive problems, such as working memory, during comprehensive assessments and make referrals for formal neurocognitive evalutions when indicated.

Implications for Research

Describing decline—particularly in terms of cognitive processes—among children being treated for ALL does not provide an explanation of the potential causal factors for this decline. Academic and social factors related to absenteeism in school and isolation from normal school-related activities, as well as the implications of stress given the diagnosis and consequent treatment, could contribute to causal mechanisms of decline. The effect of chemotherapy on the developing brain requires additional investigation to examine mechanisms for decline and point to targeted interventions.

Conclusion

Changes in survival rates for children receiving treatment for leukemia are leading to greater focus on the specific cognitive processes affected. Such knowledge can inform interventions to prevent and/or manage the deleterious effects of leukemia and suggest early referral to engage school resources. This study provides evidence that working memory declines during treatment among children undergoing chemotherapy for ALL. Female gender is also a risk factor for decline in processing speed. In this study, risk group was not predictive of decline in cognitive processes, but particular sample characteristics (few children considered to be at low risk or very high risk) may have affected this outcome.

The current study uniquely examined change over time in several cognitive processes during treatment for ALL with chemotherapy. Using latent growth curve modeling with longitudinal data collected during the course of treatment, the authors were able to model intra-individual change and obtain a slope for each participant. Examining change over time, rather than the usual approach of comparing children with ALL with other groups (e.g., siblings, healthy children, children with other tumor types or chronic conditions), showed decline from where they started. Decline does not suggest impairment but rather a difference in where the child started at the beginning of treatment. This study adds to the literature on the potential effects of chemotherapy by examining intra-individual change during treatment. These findings provide implications for the timing of potential interventions that could improve the trajectory for school achievement among survivors.

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