

A Meta-Analysis of the Neuropsychological Sequelae of Chemotherapy-Only Treatment for Pediatric Acute Lymphoblastic Leukemia

Catherine C. Peterson, PhD,^{1*} Courtney E. Johnson, MA,² Lisa Y. Ramirez, MA,² Samantha Huestis, MA,² Ahna L.H. Pai, PhD,³ Heath A. Demaree, PhD,² and Dennis Drotar, PhD³

Background. Mixed findings on the neuropsychological sequelae of chemotherapy-only treatment for pediatric acute lymphoblastic leukemia (ALL), without radiation, indicate the need for a comprehensive meta-analytic review. The purpose of the current study was to conduct a meta-analysis assessing neuropsychological and academic functioning differences between children with ALL treated solely with chemotherapy and comparison groups. **Procedures.** Thirteen articles met inclusion criteria for the meta-analysis and were analyzed using a random effects model, weighted least squares methods. **Results.** Mean effect sizes were significantly different from zero for multiple domains of intelligence and

academic achievement; processing speed; verbal memory; and some aspects of executive functioning and fine motor skills, indicating worse functioning in ALL survivors. Effect sizes for visual-motor skills and visual memory were not significantly different from zero. **Conclusions.** Results support the presence of neuropsychological and academic sequelae for ALL survivors treated solely with chemotherapy and highlight the need for ongoing follow-up of children with ALL using a standardized neuropsychological test battery and research methodology. *Pediatr Blood Cancer* 2008;51:99–104. © 2008 Wiley-Liss, Inc.

Key words: chemotherapy; leukemia; meta-analysis; neuropsychological; pediatric cancer survivor

INTRODUCTION

Research examining the neuropsychological outcomes of whole brain radiation therapy (RT) plus intrathecal (IT) chemotherapy for acute lymphoblastic leukemia (ALL) has indicated declines in nonverbal intelligence, math achievement, visual-motor integration, processing speed, attention, executive functioning, and memory [1–6]. Two meta-analytic reviews of the neuropsychological outcomes of RT [1,7] documented significantly decreased intellectual functioning in ALL survivors, as well as poorer academic achievement, attention, information processing, executive functioning, psychomotor and visuospatial skills, and memory compared to controls. Both meta-analytic reviews included children who had received RT; however, the outcomes of chemotherapy-only treatment for ALL have not been subjected to meta-analytic review. Campbell and colleagues [7] noted that their meta-analysis could not conclusively determine the impact of chemotherapy-only treatment. Thus, it is now important to describe, using meta-analytic techniques, the long-term neuropsychological sequelae of chemotherapy-only for pediatric leukemia.

Research suggests that the underlying basis for neuropsychological deficits may be the impact of radiation on white matter density, by which impaired myelination affects nondominant hemisphere functions and slowed cortical activity [8,9]. Although treatment protocols were modified so that few ALL patients receive RT, most ALL patients still receive IT chemotherapy (particularly methotrexate [MTX]), often combined with intravenous or oral chemotherapy, resulting in high doses of systemic and central nervous system (CNS)-targeted chemotherapeutic agents during critical brain development. It has been reported that IT MTX, even without RT, may be linked to white matter changes, calcifications, leukoencephalopathy, cortical atrophy, and seizures [10].

One review of neuropsychological outcomes of CNS chemotherapy concluded that two-thirds of studies indicated decreased intellectual functioning in ALL survivors receiving chemotherapy

compared to controls [10]. Numerous empirical studies of neuropsychological outcomes in ALL survivors have indicated deficits in performance IQ (PIQ) [11–14], academic achievement [13,15,16], and specific cognitive skills including processing speed, attention, visual-spatial skills, fine motor skills, and nonverbal memory [12,17–20]. Some studies, however, report only slight or no impairment [21,22]. To reconcile these mixed findings, and given evidence of neuropsychological dysfunction associated with CNS treatment for ALL [10], it is critical to synthesize available data using effect size statistics to estimate the impact of chemotherapy on intellectual, neuropsychological, and academic outcomes.

METHOD

Article Identification

We conducted literature searches using MEDLINE and PsycInfo databases and reference sections of relevant articles; additional details of search terms and inclusion/exclusion criteria can be found in the Supplementary materials. Following identification of relevant articles, each article was examined in detail by the authors to

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¹Division of Child Behavioral Health, Department of Pediatrics and Communicable Diseases, University of Michigan Medical School, Michigan; ²Department of Psychology, Case Western Reserve University, Ohio; ³Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Ohio

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*Correspondence to: Catherine C. Peterson, Division of Child Behavioral Health, University of Michigan Medical School, 1500 East Medical Center Drive, 1924 Taubman Center, Ann Arbor, MI 48109. E-mail: catpeter@med.umich.edu

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determine that they included participants who had completed chemotherapy-only treatment for pediatric ALL and a comparison group that did not receive CNS treatment. Articles had to be in English and include original empirical data sufficient to calculate effect sizes (i.e., means, standard deviations, and sample sizes for ALL and control groups). From the 160 articles, studies were excluded due to sample characteristics (i.e., did not examine a homogeneous ALL survivor sample or did not have an eligible comparison group; 40%), were published prior to 1990 (to focus on recent treatment protocols that administered CNS chemotherapy only; 25%), did not report eligible neuropsychological data (11%), or did not report any empirical data (9%). Of the 21 remaining articles, eight were excluded due to unusable data (e.g., did not report all necessary data; measures were not comparable to measures in any other study).

For 13 articles meeting inclusion criteria [11–14,16–18,20–25], the following variables were abstracted: sample size, gender, mean age, mean age at diagnosis, ethnicity, SES, medical diagnoses, treatment modalities, time since diagnosis, and means and standard deviations for cognitive or academic outcomes. A neuropsychologist verified that study measures were established neuropsychological measures (i.e., if cited in the Compendium of Neuropsychological Tests [26]) versus an investigator's own measure and classified variables into constructs. See Table I for a summary of the 13 articles and sample demographics.

Effect Size Calculations

Effect sizes were calculated using ZumaStat software [27] to compare ALL and comparison groups on outcome measures. Differences between control group means and ALL group means were divided by the pooled group standard deviations, yielding a Cohen's *d* for each construct [28]. Random effects models, weighted least squares methods, were employed for primary analyses [29]. A positive effect size indicated better performance in the control group. Cohen's classification was used to interpret effect sizes, where a mean effect size of $M = 0.20$ is considered a small effect, $M = 0.50$ is medium, and $M = 0.80$ is large.

Tests of Homogeneity (Q_T)

The test of Q_T indicates the internal consistency of study outcome groupings. A significant Q_T indicates that variability in the sample is greater than expected from sampling error alone and the data should be examined for moderating factors [30]. When Q statistics were significant, effect sizes were re-calculated excluding studies that used test normative data for their comparison group, as those samples were significantly larger than recruited control groups. If the Q_T was still significant, effect sizes were re-calculated excluding studies that used translations of tests, due to the potential for a translated test not to be comparable to the original version, thereby creating increased variance. Test norms and translations were selected for removal because they potentially decrease neuropsychological assessment reliability across studies.

Gender Analyses

Based on literature indicating increased neuropsychological sequelae for girls with ALL [31], post hoc analyses of variance (ANOVAs) were calculated if effect sizes were heterogeneous based

on the Q statistic. Two studies were identified that reported sufficient data separated by gender.

RESULTS

The overall ALL sample contained a mean of 27 participants per study (M age = 5.3 years at diagnosis; M time since treatment = 4.7 years; M age = 11.1 years at assessment). Gender breakdown was 13.6 females and 14.4 males per study. Comparison groups (excluding studies that used test norm groups for comparison groups) had a mean of 26 participants per study (M age = 12.0 years at assessment). Gender breakdown of comparison groups was 13.6 females and 14.7 males per study. Nine studies reported information regarding participant ethnicities, which was predominantly Caucasian. Specific chemotherapy protocols were described in nine studies, and all included IT chemotherapy; seven of the nine specified that patients received triple IT (TIT) chemotherapy (MTX, cytosine arabinoside, and hydrocortisone). All studies were cross-sectional.

Mean effect sizes were calculated for full scale intelligence (FSIQ), verbal IQ (VIQ), PIQ, math achievement, reading achievement, freedom from distractibility index, perceptual organization index, coding, digit span, finger tapping, Purdue pegboard (both hands), Purdue pegboard (preferred hand), trails B, and verbal memory. Table II presents weighted mean effect sizes, confidence intervals, and Q statistics for all constructs. With one exception (finger tapping), significant group differences indicated poorer functioning in the ALL group.

Intelligence

Mean effect sizes for FSIQ were significantly different from zero ($M = 0.55$, 95% CI = .27–0.83, $n = 10$), indicating that children with ALL had significantly lower FSIQ scores relative to control groups. The Q statistic for Q_T was significant ($Q_T = 22.85$, $P < 0.01$). Therefore, mean effect sizes were recalculated by eliminating three studies that utilized test norms as a comparison group. The resulting effect size was larger ($M = 0.76$, 95% CI = 0.26–1.26, $n = 7$), but the Q still indicated heterogeneity ($Q_T = 22$, $P < 0.01$). Next, the three studies utilizing foreign translations of the measure were excluded; the recalculated mean effect size was still significantly different from zero ($M = 0.76$, 95% CI = 0.42–1.12, $n = 7$), and the Q was not significant. Results suggest that ALL survivors demonstrated significantly lower IQ scores than controls.

Similar results were found for index scores of the Wechsler intelligence measures [32–35]. Children with ALL had significantly lower VIQ and PIQ scores, with a medium mean effect size significantly different from zero. The Q statistic was significant for VIQ and PIQ and remained significant excluding norms. The freedom from distractibility index and perceptual organization index scores were significantly different from zero (Q statistics not significant), indicating lower scores in the ALL group. The verbal comprehension index did not significantly differ between groups ($n = 2$).

Subtest-level findings were inconsistent. Effect sizes were significantly different from zero for digit span and coding but not for arithmetic, block design, similarities, or vocabulary. Q statistics were significant for arithmetic, block design, and coding; when

TABLE I. Summary of Demographic Characteristics From Articles Included in Meta-Analysis

Source	ALL Survivors					Controls			
	N	Mean age (years) at diagnosis	Mean time (years) since treatment	Mean age (years) at evaluation	% Female	Group type	N	Mean age (years) at evaluation	% Female
Kaemingk et al. [16]	15	5.44	4.4	12.62	40	a, b	15	11.97	40
Schatz et al. [20]	8	7	6.7	13.9	75	a, b	24	17.4	58
Brown et al. [25]	11	NR	1	7.55	64	a	12	9.02	50
Hill et al. [17]	10	1–5 years	≥3	10.3	NR	a, b	10	10.1	NR
Lesnick et al. [18]	10	1–5 years	≥3	6.9–13.5	60	a, b	10	6.0–13.0	60
Raymond-Speden et al. [13]	21	4.1	4.9	9.4	43	b	21	10.6	48
Giralt et al. [12]	29	5.48	≥3	11.37	48	a, c	46	11.46	37
von der Weid et al. [14]	132	4.8*	≥2	14.7*	50	c	100	15.8*	46
Rodgers et al. [21]	17	4	5	9.72	35	a	17	11.5	59
Kingma et al. [23]	17	3.5*	≥5	9.3*	41	d	225	NR	NR
Kingma et al. [22]	20	3.4*	NR	10.3*	45	d	225	NR	NR
Schatz et al. [24]	9	6.9	6.9	13.9	78	a, b	9	14.3	78
Brown et al. [11]	20–43	4.3	3.8	11	43	d	**	NR	NR

ALL, acute lymphoblastic leukemia; NR, not reported. Control group types: a, healthy, family member (e.g., sibling); b, healthy, non-family (e.g., friend, neighbor, classmate); c, cancer patient, non-CNS tumor; d, test normative sample; *reported median versus mean for age variables; therefore, these studies were excluded from mean age calculations of overall sample; **control N varied depending on test used: Wechsler Intelligence Scale for Children (WISC) normative sample = 2,200; Woodcock–Johnson (WJ) normative sample = 3,245; Beery Test of Visual-Motor Integration (VMI) normative sample = 2,734.

arithmetic and coding were re-analyzed excluding translations, the recalculated arithmetic mean effect size was not significant, whereas the coding recalculated mean effect size was significant.

Academic Achievement

Effect sizes were significantly different from zero for math achievement and reading achievement. Results suggest that ALL survivors demonstrated significantly lower academic achievement than comparison groups on both achievement domains.

Neuropsychological Constructs

Results were inconsistent for measures of visual-motor integration, fine motor skills, and reaction time. Effect sizes were significantly different from zero on the Purdue pegboard task for both hands and preferred hand but not for Assembly. Q statistics were not significant. Effect sizes for VMI were not significant. Effect sizes were significantly different from zero for the finger tapping test, but effect sizes were negative, indicating that the ALL group scored higher on this test than the comparison groups. Children with ALL performed significantly worse on Trails B (a measure of executive functioning) but not Trails A (a measure of fine motor tracking). Verbal fluency comparison was not significant. The effect size for verbal memory was significantly different from zero, indicating that children with ALL performed more poorly than controls. Visual memory effect sizes were not significant.

Gender Comparisons

Post hoc ANOVAs on IQ constructs were conducted to explore potential gender differences [31]. Mean effect sizes were signifi-

cantly different from zero for FSIQ ($M = -0.57$, 95% CI = -0.86 – -0.28 , $n = 2$), PIQ ($M = -0.49$, 95% CI = -0.78 – -0.19 , $n = 2$), and VIQ ($M = -0.51$, 95% CI = -0.80 – -0.21 , $n = 2$), indicating that girls performed worse than boys.

DISCUSSION

These findings present empirical support, using effect size statistics, for a pattern of neuropsychological sequelae of modern chemotherapy-only treatment protocols. These effect size data support research documenting neuropsychological late effects of childhood cancer, particularly given recent reports of no impairment or only mild impairment on select outcome measures following chemotherapy [22]. Results suggest that intellectual functioning does appear to be affected in ALL patients, even without RT, particularly in the areas of perceptual reasoning skills, working memory, and processing speed. Verbal subtests, however, were not significantly different between the groups, suggesting that select verbal skills may be spared in ALL survivors. This pattern of strengths and weaknesses is consistent with previously reviewed evidence [10], but this meta-analytic review provides synthesis of effect sizes from multiple studies supporting this pattern of strengths and weaknesses in ALL survivors.

Findings indicated that ALL survivors exhibit difficulty attaining academic progress in both math and reading. Although previous research has focused on math achievement [16], these data suggest that reading achievement also may be affected. Neuropsychological findings were mixed, with some evidence of fine motor, executive function, and verbal memory weaknesses in ALL survivors. These results, however, were based on very small samples and therefore, should be interpreted very cautiously. Post hoc analyses examining gender differences on intelligence tests also were based on small samples, so these findings must be interpreted with extreme caution. Nonetheless, our finding was consistent with reports that girls may

TABLE II. Weighted Mean Effect Sizes; 95% Confidence Intervals; and Q Statistics for Neuropsychological Constructs

Measure/construct	N of studies	Weighted M ES	95% CI	Q
General intelligence	10	0.55**	0.27–0.83	22.85**
Excluding normative data [†]	7	0.76**	0.26–1.26	22**
Excluding translations [†]	7	0.76**	0.42–1.12	10.72
Verbal IQ	6	0.46**	0.11–0.81	18.06**
Excluding normative data	3	0.86	0.09–1.81	14.90**
Excluding translations	3	0.87	0.06–1.80	13.59**
Performance IQ	6	0.42*	0.03–0.81	23.58**
Excluding normative data	3	0.64	0.27–1.55	14.30**
Excluding translations	3	0.73*	0.14–1.32	5.78
Freedom from distractibility index	2	0.54**	0.25–0.83	0.13
Perceptual organization index	2	0.70**	0.40–0.99	0.96
Verbal comprehension index	2	0.48	0.38–1.33	5.73*
Arithmetic (Wechsler subtest)	3	0.40	0.19–0.99	6.75*
Excluding translations	2	0.66	0.26–1.58	3.23
Block design (Wechsler subtest)	2	0.27	0.34–0.88	4.07*
Coding (Wechsler subtest)	4	0.48	0.02–0.98	9.73*
Excluding translations	3	0.70**	0.27–1.12	2.28
Digit span (Wechsler subtest)	6	0.28*	0.04–0.52	7.35
Similarities (Wechsler subtest)	2	0.34	0.14–0.81	2.56
Vocabulary (Wechsler subtest)	2	0.27	0.16–0.70	2.19
Math achievement	5	0.61**	0.20–1.03	7.88
Reading achievement	5	0.65*	0.03–1.27	17.54**
Excluding normative data	4	0.87**	0.48–1.26	2.31
VMI	4	0.37	0.19–0.93	13.95**
Finger tapping (preferred hand)	2	–0.35*	–0.68––0.01	0.94
Purdue pegboard (assembly)	2	–0.11	–0.45–0.22	0.09
Purdue pegboard (both hands)	2	0.38*	0.04–0.71	0.04
Purdue pegboard (preferred hand)	3	0.39*	0.08–0.69	1.94
Verbal fluency	2	0.41	0.06–0.88	0.86
Trails A	3	0.32	–0.24–0.87	4.65
Trails B	3	0.70**	0.18–1.23	3.97
Verbal memory	2	1.16**	0.54–1.79	1.06
Visual memory	2	1.03	0.64–2.70	6.84**

ES, effect size; CI, confidence interval; IQ, intelligence quotient; VMI, Beery test of visual-motor integration; * $P < 0.05$; ** $P < 0.01$; [†]when the Q statistic indicated significant heterogeneity, analyses were re-run excluding either: (a) studies that used normative data as their comparison group versus a recruited control sample, or (b) studies that used translated versions of tests originally created in English, in order to reduce the potential for heterogeneity whenever possible. All data that could be calculated are presented.

be at greater risk for neuropsychological late effects than boys [31], warranting further investigation into gender differences in neuropsychological development.

The limitations of the meta-analysis reflect the state of the literature, particularly the limited number of studies that could be included due to methodological variability. We could not perform post hoc ANOVAs on potential risk factors of age at diagnosis and time since diagnosis, as few studies presented data separated into groups by age at diagnosis or time since diagnosis. Further, several studies were excluded due to the use of translated or newly developed measures that were not comparable to established neuropsychological measures. Other studies used heterogeneous samples such as a cancer sample that included another leukemia subtype or lymphoma. We focused on a homogeneous ALL sample, despite the loss of usable data, to facilitate more precise understanding of neuropsychological sequelae of a specific treatment component for ALL. A meta-analysis also can be limited by the impact of publication bias, which may attenuate the strength of

effects found. It was not possible to illustrate publication bias for visual examination, however, as the number of studies was far too small for accurate interpretation [30].

These findings have bearing on future research and clinical practice in the management of neuropsychological sequelae of pediatric ALL. Treatment intensity may be an important moderator of outcomes, as multiple IT agents (e.g., TIT chemotherapy) may impact neuropsychological sequelae. It has been proposed that IT cytosine arabinoside may actually exacerbate the neurotoxicity of IT MTX [12]. Because few studies reported treatment protocol details, we could not examine treatment intensity as a moderator. Research also should examine other treatment modalities that have been implicated in neuropsychological dysfunction, such as corticosteroids (e.g., dexamethasone) [36]. Finally, interventions need to be studied, such as cognitive remediation [37], psychostimulant medication [38], and intensive tutoring [39].

Future research also must use carefully matched comparison groups, as studies may be of limited generalizability if they use

normative data as a comparison group, newly created measures, or IQ tests only [2,10]. It is important to develop a standardized battery within each culture to obtain the best estimate of neuropsychological sequelae in a culturally fair manner. Finally, studies from other cultures may reflect a different medical treatment protocol or some unique aspect of supportive intervention (e.g., more intense tutoring) during cancer treatment. Future studies may benefit from examining supportive academic interventions in more detail as a potential moderator.

These findings inform clinical care, as individualized neuropsychological monitoring and academic intervention (e.g., special education, classroom accommodations) may enhance functional outcomes for ALL survivors including graduation and job attainment rates and long-term adaptive skills to transition to adulthood. A standardized neuropsychological test battery is critical; one has been proposed [40], although widespread implementation (particularly internationally) may be hindered by obstacles such as variable institutional commitment to neuropsychological assessment and insurance reimbursement issues. Finally, baseline testing of all young ALL patients is needed to track neuropsychological and academic skills over time to facilitate early intervention and prevent academic failure.

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