Brief Report: Effect of Intravenous Methotrexate Dose and Infusion Rate on Neuropsychological Function One Year after Diagnosis of Acute Lymphoblastic Leukemia

Marissa E. Carey,[1] PhD, Marilyn J. Hockenberry,[2,3] PhD, Ida M. Moore,[4] DNS, John J. Hutter,[5] MD, Kevin R. Krull,[2,6] PhD, Alice Pasvogel,[4] PhD, and Kris L. Kaemingk,[5] PhD

[1]Department of Behavioral Medicine and Psychiatry, West Virginia University, [2]Department of Pediatrics, Baylor College of Medicine, [3]Texas Children's Cancer Center, [4]College of Nursing, [5]Department of Pediatrics, The University of Arizona, and [6]Texas Children's Hospital

Objective To compare the effects of two intravenous (IV) methotrexate (MTX) infusion protocols on cognitive function in children newly diagnosed with acute lymphoblastic leukemia (ALL). **Methods** We compared 19 children treated with 1 g/m^2 of IV MTX over 24 hr (Group 1) to 13 children treated with 2 g/m^2 of IV MTX over 4 hr (Group 2) on measures of working memory, nonverbal, and verbal skills shortly after diagnosis (Time 1) and 1 year later (Time 2). **Results** A significant Group×Time interaction was found for a composite measure of working memory with Group 2 declining from Time 1 to Time 2. Group 2 performed significantly worse than Group 1 on a composite measure of nonverbal skills at both time points. **Conclusions** Findings suggest that difficulties in working memory and nonverbal skills may be evident during the first year of treatment for ALL and that severity may be dependent on IV MTX dose and/or infusion rate.

Key words acute lymphoblastic leukemia; chemotherapy; methotrexate; neuropsychology.

There is accumulating evidence that treatment protocols for acute lymphoblastic leukemia (ALL) have long-term effects on cognitive function despite the elimination of cranial radiation therapy (CRT) from standard treatment. Long-term difficulties in visual-perceptual and attention skills are most commonly reported (Moore, 2005), although language-related difficulties have also been described (Brown, Sawyer, Antoniou, Toogood, & Rice, 1999).

Currently, majority of children treated for ALL receive central nervous system (CNS) prophylaxis with a combination of intrathecal (IT) and systemic chemotherapy (Margolin, Steuber, & Poplack, 2002). Methotrexate (MTX) is the most widely used antimetabolite in the treatment of childhood cancers and is a critical component of ALL treatment (Margolin et al., 2002). ALL treatment protocols typically have three phases: induction (weeks 1–4), consolidation (weeks 5–32), and maintenance (weeks 33–130). IT MTX is administered in age-titrated doses directly to the CNS via the cerebral spinal fluid (Margolin et al., 2002), but the optimal dose of intravenous (IV) MTX has yet to be established (Moe & Holen, 2000). IV MTX is introduced through the blood stream and is administered in a wide range of doses, rates of infusion, and number of infusions (Moe & Holen, 2000). MTX has been associated with acute neurotoxicity as well as with long-term cognitive difficulties in ALL survivors (Margolin et al., 2002). Lower overall IQ has been linked to a single, high-dose IV MTX infusion compared to a single, standard dose IV MTX infusion in female ALL survivors, but only when followed with CRT (Waber, Tarbell, Kahn, Gelber, & Sallan, 1992). To our knowledge, no studies have been published that compare the effects of IV MTX infusion rates on cognitive function.

All correspondence concerning this article should be addressed to Marissa E. Carey, West Virginia University, Department of Behavioral Medicine and Psychiatry, 930 Chestnut Ridge Road, P.O. Box 9137, Morgantown, West Virginia 26505. E-mail: mcarey@hsc.wvu.edu.

Journal of Pediatric Psychology 32(2) pp. 189–193, 2007
doi:10.1093/jpepsy/jsj114
Advance Access publication May 4, 2006

The purpose of the present study, therefore, was to investigate the effects of a short, higher dose IV MTX infusion to a long, lower dose IV MTX infusion on working memory, nonverbal, and verbal skills in children newly diagnosed with ALL. Children were randomly assigned to receive either 1 g/m^2 of IV MTX over 24 hr (Group 1) or 2 g/m^2 of IV MTX over 4 hr (Group 2) for a total of six infusions during the consolidation phase of treatment. We compared group performance on selected measures shortly after diagnosis and approximately 1 year later. Because some children had already started consolidation at the time of the first evaluation, we predicted that there would be a significant effect of treatment group and time on working memory and nonverbal skills, given the long-term difficulties in attention and visual-perceptual skills often reported. It was expected that Group 1 would perform better than Group 2 at both time points, but that both groups' performances would decline over time. We also predicted that verbal skills would be equivalent between groups and remain stable over time.

Methods

Participants

Study participants were recruited through a major university hospital pediatric hematology/oncology clinic and a major children's cancer center in the southwestern and southern portions of the United States, respectively. Children enrolled in Pediatric Oncology Group (POG) Protocol 9904 (ALinC 17 for low-risk ALL) or 9905 (ALinC 17 for standard risk ALL), who were also participating in a longitudinal study examining cognitive development in children treated for ALL, were included in these analyses. These POG protocols were designed in conjunction to compare the efficacy and toxicity of a short MTX infusion (2 g/m^2 over 4 hr) to a long MTX infusion (1 g/m^2 over 24 hr) during the consolidation phase of treatment. At the time of protocol enrollment, each child was randomly assigned to one of these infusion protocols. All patients received CNS prophylaxis with IT MTX at age-titrated doses according to the same dose schedule. None of these children received CRT. All children who met eligibility criteria were invited to participate in the cognitive study. Due to the Health Insurance Portability and Accountability Act (HIPAA) of 1996 privacy rules, data were not collected on the children who declined to participate in the cognitive study. However, very few individuals refused at either site. Exclusionary criteria were non-English-speaking children and previous diagnoses of learning disability, attention-deficit hyperactivity disorder, mental retardation, psychiatric disorder, neurological disorder, or traumatic brain injury associated with an alteration in consciousness. Protocols were approved by the Institutional Review Boards of both institutions. Informed consent was obtained from all parents, and assent for participation in the cognitive study was obtained from the children.

Table I. Patient Characteristics

	Group 1	Group 2
Age at diagnosis (in years)	6.60 (±3.41)	7.75 (±3.47)
Age at Time 1 (in years)	6.71 (±3.41)	7.88 (±3.44)
Age at Time 2 (in years)	7.94 (±3.38)	9.05 (±3.58)
Days since diagnosis at Time 1	38.95 (±19.74)	46.54 (±16.69)
Days since diagnosis at Time 2	488.68 (±58.53)	475.38 (±51.39)
Number of IT MTX doses at Time 1	2.47 (±0.77)	2.62 (±0.77)
Number of IT MTX doses at Time 2	11.42 (±0.77)	11.23 (±0.83)
Males	5	6
Females	14	7
Low-risk level	8	5
Standard risk level	11	8
Mother's education (in years)	14.00 (2.76)	13.45 (1.75)

IT MTX, intrathecal methotrexate.

Seventy-eight children were enrolled in the cognitive study between June 2000 and December 2002. Fifty-nine of them were enrolled in POG Protocol 9904 or 9905, and 43 of those children completed Time 1 and Time 2 evaluations. Of the 16 who did not complete Time 1 and Time 2 evaluations, 9 did not complete evaluations due to scheduling difficulties, 4 were lost to follow-up, 1 relapsed, 1 died, and 1 moved out of the area. In order to minimize variability, only those who completed Time 1 evaluations within 90 days of diagnosis (N = 39) and whose Time 2 evaluation occurred within 1 SD of the mean number of days between evaluations (M = 437.87; SD = 125.25) were included in these analyses. Hence, we compared the performances of 32 children: 19 children in Group 1 and 13 children in Group 2. There were no differences between the groups with respect to patient characteristics (Table I).

Evaluation Procedure and Measures

Each child completed evaluations at Time 1 and Time 2. Time 1 evaluations were scheduled as soon as a child was medically stable, which typically followed the completion of induction therapy. The Wechsler Primary and Preschool Scale of Intelligence—Revised (WPPSI-R) (Wechsler, 1989) was administered to children aged 3–5 years (Time 1, N = 13; Time 2, N = 10). The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) was administered to children aged 6 years and more. Due to the small sample size and to minimize the number of statistical comparisons, composite scores

were created to assess working memory, nonverbal, and verbal skills. Pearson product correlations were computed for measures making up each composite, and correlations ($r \geq .395$, $p \leq .025$) between measures support the domain clusters. Age standard scores were transformed into *Z*-scores and then averaged. The working memory composite score included (a) Stanford-Binet Intelligence Scale—4th Edition (SBIS-IV) Memory for Sentences (Thorndike, Hagen, & Sattler, 1986), which is a sentence repetition task, and (b) SBIS-IV Bead Memory (Thorndike et al., 1986), which is a visual working memory task requiring immediate reproduction of bead sequences. The nonverbal composite score included (a) Wechsler Block Design (Wechsler, 1989, 1999), which assesses visual-perceptual organization skills using blocks, and (b) Beery Developmental Test of Visual-Motor Integration—4th Edition (VMI) (Beery, 1997), which is a design copying task. The verbal composite score included (a) Wechsler Vocabulary (Wechsler, 1989, 1999), which assesses expressive language skills, and (b) Peabody Picture Vocabulary Test—3rd Edition (PPVT-III) (Dunn & Dunn, 1997), which assesses receptive language skills.

Data Analysis

The SASJMP6 statistical software package (SAS Institute, 2005) was used for data analysis. Within- and between-group comparisons were performed using mixed models analyses due to the variability in days since diagnosis at Time 1 and Time 2 for both groups. Group was entered as a fixed effect. Time and Group × Time were entered as random effects. The dependent variables were the working memory, nonverbal, and verbal composite scores. The significance level for these analyses was set at $p < .05$.

Results

Results of the mixed models analyses revealed (a) a significant main effect of Group for nonverbal, $F(1, 30) = 5.338$, $p = .0352$, $d = .451$, with Group 1 performing better than Group 2 at both time points; and (b) a significant Time×Group interaction for working memory, $F(1, 30) = 9.548$, $p = .004$, $r = .153$, with Group 1 performing better from Time 1 to Time 2, while Group 2 performed worse over time. No other significant effects were found. Scores are presented in Table II. Because mean scores for both groups at Time 1 and Time 2 were in the average range for all measures, follow-up Mann–Whitney *U* tests were conducted to determine whether the proportion of children with performances ≤–1.0 *SD* from the mean was significantly different between the two groups. No significant differences were found for the three composite measures at either time point. However, there was a non-significant trend ($p = .058$) for SBIS-IV Bead Memory, with Group 2 having a significantly greater proportion of children (38.5%) performing below the mean compared to Group 1 (10.5%) at Time 2.

Table II. Group Means and Standard Deviations for Composite and Subtest Scores at Time 1 and Time 2

Composite/Subtest	Group (g/m^2)	Time 1 Mean (*SD*)	Time 2 Mean (*SD*)
Wechsler Full Scale IQ	1	105.84 (11.99)	107.05 (15.52)
(*M* = 100, *SD* = 15)	2	102.38 (10.54)	101.15 (14.43)
Working memory[a]	1	–0.24 (1.01)	0.03 (.74)
(*M* = 0, *SD* = 1)	2	0.26 (.81)	–0.36 (.61)
SBIS-IV Sentence Memory	1	50.53 (8.10)	49.32 (7.58)
(*M* = 50, *SD* = 8)	2	52.77 (5.50)	50.15 (4.26)
SBIS-IV Bead Memory	1	52.05 (10.82)	52.53 (7.78)
(*M* = 50, *SD* = 8)	2	51.77 (9.17)	47.38 (7.10)
Nonverbal[b]	1	0.37 (.52)	0.38 (.80)
(*M* = 0, *SD* = 1)	2	–0.01 (.64)	–0.14 (.70)
Wechsler Block Design	1	12.00 (1.89)	11.84 (2.89)
(*M* = 10, *SD* = 3)	2	10.77 (2.09)	10.31 (2.72)
VMI	1	101.21 (8.80)	102.05 (13.69)
(*M* = 100, *SD* = 15)	2	95.77 (11.88)	94.23 (10.32)
Verbal	1	–0.06 (.63)	0.10 (.84)
(*M* = 0, *SD* = 1)	2	0.32 (1.06)	0.15 (1.08)
PPVT-III	1	102.05 (10.46)	103.32 (12.20)
(*M* = 100, *SD* = 15)	2	107.15 (17.06)	106.54 (15.13)
Wechsler Vocabulary	1	9.21 (2.57)	9.95 (3.05)
(*M* = 10, *SD* = 3)	2	10.46 (3.21)	9.62 (3.66)

[a]Time×dose interaction effect at $p < .05$.

[b]Main effect of Group at $p < .05$.

M, arithmetic mean; *SD*, standard deviation.

SBIS-IV, Stanford-Binet Intelligence Scale—4th Edition; VMI, Beery Developmental Test of Visual-Motor Integration—4th Edition; PPVT-III, Peabody Picture Vocabulary Test—3rd Edition.

Discussion

Our findings suggest that difficulties in working memory and nonverbal skills may be evident during the first year of treatment for ALL and that the severity of these difficulties appear to be dependent on IV MTX dose and/or infusion rate. These findings are consistent with our hypotheses and with previous late effects literature, suggesting that attention and visual-perceptual skills are compromised in some children treated for ALL (Moore, 2005). It is not clear if these difficulties are permanent. These children are being followed, and future reports will try to elucidate the nature of these difficulties over time.

These results are in contrast to the findings of Waber et al. (1992), who did not report any differences between the neuropsychological performances of ALL survivors treated with high-dose IV MTX (33 or 4 g/m^2) and standard dose IV MTX (40 mg/m^2) in the absence of follow-up CRT. However, children in their study received only a single infusion of IV MTX during the induction phase of treatment. The rate of infusion was not reported and so could not be compared with the current findings. In our study, children received six IV MTX infusions during the consolidation phase of therapy. While it is unclear if the small dose difference between groups is clinically meaningful, pharmacokinetic differences have been reported between short (4–6 hr) and long (24–36 hr) MTX infusions in the treatment of ALL (Borsi, Schuler, & Moe, 1988; Wolfrom et al., 1993). Because the children receiving lower dose IV MTX (1 g/m^2) in our study also received much longer 24-hr infusions (compared to the 4-hr infusions of the 2 g/m^2 group), differences found between our groups may be related to differences in the duration of infusions.

This study is limited by a small sample size. Despite this, we were able to detect group differences and an interaction effect. Follow-up study with a larger sample is needed, preferably using the same protocols, to validate the current findings. The national study recently closed accrual of new patients to these protocols, and, to date, there have been no published reports comparing the efficacy of the two MTX infusion protocols. Ultimately, if treatment efficacy is equivalent for survival, then the impact on cognitive function needs to be considered to ensure the best treatment outcomes. While work in this important area continues, it is recommended that practitioners follow the neuropsychological function of children with ALL from the time of diagnosis, because early identification and intervention may curb or even prevent long-term difficulties (Moore et al., 2000).

Acknowledgments

This work was supported by the National Institutes of Health (HD37816 and NR04905). A portion of these data was presented at the 2nd Annual Conference of the American Psychosocial Oncology Society in Phoenix, Arizona (January 2005). The authors would like to thank Sheryl Reminger, PhD, and Marc Haut, PhD, for their feedback during manuscript preparation and Gerald Hobbs, PhD, for his help with statistical analyses.

Received August 3, 2005; revision received November 16, 2005 and February 2, 2006; accepted March 20, 2006

References

Beery, K. E. (1997). *The Beery-Buktenica Developmental Test of Visual-Motor Integration: Administration, Scoring, and Teaching Manual* (4th rev. ed.). Parsippany, NJ: Modern Curriculum Press.

Borsi, J. D., Schuler, D., & Moe, P. J. (1988). Methotrexate administered by 6-h and 24-h infusion: a pharmacokinetic comparison. *Cancer Chemotherapy and Pharmacology*, *22*, 33–35.

Brown, R. T., Sawyer, M. G., Antoniou, G., Toogood, I., & Rice, M. (1999). Longitudinal follow-up of the intellectual and academic functioning of children receiving central nervous system-prophylactic chemotherapy for leukemia: a four-year final report. *Journal of Developmental and Behavioral Pediatrics*, *20*, 373–377.

Dunn, L. M., & Dunn, L. M. (1997). *Examiner's Manual for the Peabody Picture Vocabulary Test—Third Edition*. Circle Pines, MN: American Guidance Service.

Margolin, J. F., Steuber, C. P., & Poplack, D. G. (2002). Acute lymphoblastic leukemia. In P. A. Pizzo, & D. G. Poplack (Eds.), *Principles and practice of pediatric oncology* (4th ed., pp. 489–544). Philadelphia, PA: Lippincott Williams and Wilkins.

Moe, P. J., & Holen, A. (2000). High-dose methotrexate in childhood ALL. *Pediatric Hematology and Oncology*, *17*, 615–622.

Moore, B. D., 3rd. (2005). Neurocognitive outcomes in survivors of childhood cancer [see comment]. *Journal of Pediatric Psychology*, *30*, 51–63.

Moore, I. M., Espy, K. A., Kaufmann, P., Kramer, J., Kaemingk, K., Miketova, P., et al. (2000). Cognitive consequences and central nervous system injury following treatment for childhood leukemia. *Seminars in Oncology Nursing, 16*, 279–290; discussion 279–291.

Thorndike, R. L., Hagen, E. P., & Sattler, J. M. (1986). *The Stanford-Binet Intelligence Scale: Fourth Edition*. Chicago, IL: Riverside Publishing Co.

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

Wechsler, D. (1989). *Wechsler Preschool and Primary Scale of Intelligence—Revised Manual*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence Manual*. San Antonio, TX: Harcourt Brace & Co.

Wolfrom, C., Hartmann, R., Fengler, R., Bruhmuller, S., Ingwersen, A., & Henze, G. (1993). Randomized comparison of 36-hour intermediate-dose versus 4-hour high-dose methotrexate infusions for remission induction in relapsed childhood acute lymphoblastic leukemia [see comment]. *Journal of Clinical Oncology*, *11*, 827–833.