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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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Comparison of Neurocognitive Functioning in Children Previously Randomly Assigned to Intrathecal Methotrexate Compared With Triple Intrathecal Therapy for the Treatment of Childhood Acute Lymphoblastic Leukemia

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ABSTRACT

Purpose

For the majority of children with acute lymphoblastic leukemia (ALL), CNS prophylaxis consists of either intrathecal (IT) methotrexate or triple IT therapy (ie, methotrexate with both cytarabine and hydrocortisone). The long-term neurotoxicities of these two IT strategies have not yet been directly compared.

Patients and Methods

In this multisite study, 171 children with standard-risk ALL, age 1 to 9.99 years at diagnosis, previously randomly assigned to IT methotrexate ($n = 82$) or to triple IT therapy ($n = 89$) on CCG 1952, underwent neurocognitive evaluation by a licensed psychologist at a mean of 5.9 years after random assignment.

Results

Patients who received IT methotrexate had a mean Processing Speed Index that was 3.6 points lower, about one fourth of a standard deviation, than those who received triple IT therapy ($P = .04$) after analysis was adjusted for age, sex, and time since diagnosis. Likewise, 19.5% of children in the IT methotrexate group had a Processing Speed Index score in the below-average range compared with 6.9% in the triple IT therapy group ($P = .02$). Otherwise, the groups performed similarly on tests of full-scale intelligence quotient, academic achievement, attention/concentration, memory, and visual motor integration. The association of treatment with measures of cognitive functioning was not modified by sex or age at diagnosis. In the post-therapy period, there were no group differences in special education services, neurologic events, or use of psychotropic medications.

Conclusion

This study did not show any clinically meaningful differences in neurocognitive functioning between patients previously randomly assigned to IT methotrexate or triple IT therapy except for a small difference in processing speed in the IT methotrexate group.

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INTRODUCTION

The introduction of presymptomatic CNS therapy during the 1970s was a major factor in the transformation of childhood acute lymphoblastic leukemia (ALL) to a highly treatable disease.¹ CNS therapy was originally delivered with cranial radiation at 18 to 24 Gy, which had the undesired effects of diminished intelligence quotient (IQ), poor academic functioning, subsequent cancers, and endocrinopathies.²⁻⁴ Through a series of trials, it was determined that intrathecal (IT) chemotherapy could replace cranial radiation for the majority of children with ALL.⁵⁻⁷ Two primary IT medication

strategies emerged: IT methotrexate and triple IT therapy (ie, methotrexate with both cytarabine and hydrocortisone). Assignment to one of these preparations varied by treatment protocol, cooperative group, and treatment center.

Only recently have the therapeutic efficacies of these two strategies been compared directly. In a Children's Cancer Group (CCG) study of 1,018 patients with childhood ALL, Matloub et al⁸ concluded that triple IT therapy was associated with a 6-year cumulative incidence of isolated CNS relapse of $3.4\% \pm 1.0\%$ compared with $5.9\% \pm 1.2\%$ for IT methotrexate ($P = .004$), but the therapies had similar event-free survival rates. Interestingly, triple IT

Table 1. Comparison of Participants to Eligible Nonparticipants

Characteristic	Participants (n = 171)		Eligible Non- participants (n = 356)		P*
	No.	%	No.	%	
Age at diagnosis, years					
Mean	4.2		4.0		.23
SD	2.0		1.7		
Years between diagnosis and start of the study					
Mean	5.9		6.1		.06
SD	1.1		1.1		
Sex					
Female	77	45	166	47	.73
Male	94	55	190	53	
Therapy					
IT methotrexate	82	48	177	50	.70
Tripe IT therapy	89	52	179	50	
Secondary random assignment					
Mercaptopurine	76	44	180	51	.19
Thioguanine	95	56	176	49	

Abbreviations: SD, standard deviation; IT, intrathecal.

*By t test or χ^2 test.

therapy had worse overall survival rates, because the salvage rate after bone marrow relapse was worse than after CNS relapse. These results suggest that triple IT therapy may be particularly useful for patients with a higher risk of CNS relapse (eg, T-cell phenotype) if more effective systemic therapy is given as well.

With advances such as effective CNS prophylaxis, the vast majority of children with ALL are expected to become long-term survivors. The recently completed US cooperative trial CCG 1991, in which all patients received IT methotrexate, reported 4-year event-free survival rates approaching 90% and overall survival rates of approximately 95% for patients with standard-risk ALL.⁹ Therefore, the effect of different therapies on future quality of life has increasingly been considered as a critical factor in the selection of optimal treatment.

Unfortunately, multiple long-term studies suggest that survivors of childhood ALL who did not receive cranial radiation still may develop meaningful deficits in neurocognitive function.¹⁰⁻¹⁵ Investigators have consistently identified difficulties in attention, working

memory, processing speed, mathematics, and visual motor integration, but the exact etiology of these deficits has yet to be established. Exposure to IT medications is a possible contributing factor. Both IT methotrexate and IT cytarabine are associated with potential acute neurotoxicity, including stroke-like syndromes, myelopathy, encephalopathy, and seizures,^{16,17} and also may have long-term effects. A compelling question is whether the addition of cytarabine and hydrocortisone to IT methotrexate is associated with worse long-term toxicity.

We evaluated neurocognitive functioning in patients previously randomly assigned to IT methotrexate versus triple IT therapy on legacy CCG 1952, from which Matloub et al⁸ analyzed event-free survival and overall survival outcomes. We hypothesized that triple IT therapy is associated with greater neurocognitive impairment than IT methotrexate, especially in processing speed, attention, memory, and visual motor integration, and that younger age and female sex affect the association between IT preparation and neurocognitive functioning.

PATIENTS AND METHODS

Study Population

We conducted a cross-sectional study of patients at limited institutions who were previously enrolled and randomly assigned on CCG protocol 1952, which was open between May 1996 and February 2000. Eligible patients had B-lineage or T-lineage ALL that satisfied National Cancer Institute criteria for standard risk (ie, age at diagnosis 1.0-9.99 years and presenting WBC $< 50 \times 10^9/L$).¹⁸ The therapeutic protocol consisted of a 2×2 factorial design, in which participants were assigned randomly to either IT methotrexate or triple IT therapy as CNS-directed therapy and to either oral mercaptopurine or thioguanine as the maintenance thiopurine. Maintenance duration was 20 months for girls and 32 months for boys; thus, girls received 19 IT injections, and boys received 23 injections during the entire treatment course. For all patients, prednisone was given in induction and maintenance; dexamethasone was given in the delayed-intensification phases.⁸

Patients were eligible for participation in the neurocognitive follow-up study if they were diagnosed and enrolled on CCG 1952 at one of the 22 designated limited-institution sites (Appendix, online only). Additional eligibility requirements included the following: continuous remission, no history of CNS leukemia (thus, no cranial radiation), ≥ 1 year since cessation of therapy, age at evaluation of 6 to 16.99 years, no history of pre-existing developmental disorders (eg, trisomy 21, developmental delay), and no history of

Table 2. Neuropsychological Evaluation

Neuropsychological Domain	Test	Measure	Evaluation	
			Normative Mean	SD
Intelligence	WISC-IV	Intelligence quotient	100	15
Academic achievement	WIAT-II-A	Reading, spelling, math	100	15
Processing Speed	WISC-IV processing speed index		100	15
Visual motor integration	VMI, fifth edition		100	15
Attention/concentration	CPT II	Reaction time, omissions, commissions, variability	50*	10
Memory	CMS	General memory index, visual immediate index standard score,	100	15
	WISC IV working memory index	verbal immediate standard score		

Abbreviations: SD, standard deviation; WISC-IV, Wechsler Intelligence Scale for Children, fourth edition; WIAT-II-A, Wechsler Individual Achievement Test, second edition, abbreviated; VMI, Beery Developmental Test of Visual Motor Integration; CPT II, Conners' Continuous Performance Test II; CMS, Children's Memory Scale.

*Higher scores indicated worse impairment.

very low birth weight (< 1,500 g). The age restriction was chosen to correspond to the validated age range of the standardized neuropsychological instruments used in the evaluation. In addition, individuals were excluded if they had been nonrandomly assigned to more intensive therapy because of unfavorable cytogenetic findings or a slow response after induction.

Five hundred twenty-seven patients were enrolled on the therapeutic study at one of the participating sites and were confirmed to meet the inclusion and exclusion criteria for this study. Of these, 171 patients consented and completed the evaluation. Of the remaining 356 patients, 144 were lost to follow-up and could not be traced, 184 refused, and 28 were never offered participation. The 171 participants were similar to the 356 eligible nonparticipants in terms of age at diagnosis, elapsed time since diagnosis, sex, and therapeutic random assignments (Table 1).

The institutional review board of each participating center approved the protocol and study documents. Informed consent, and assent if indicated, was obtained from all participants.

Measures

Participants underwent a comprehensive, half-day, neurocognitive assessment supervised by a licensed psychologist. This evaluation was paid by research funds and was at no cost to the patient. The test battery was based on a previous CCG study, which successfully utilized previous editions of almost all the same tests in a longitudinal study of the neurobehavioral effects of intermediate risk ALL and its therapy.¹⁹ The neurocognitive functioning evaluation included, among others, the following tests: Wechsler Intelligence Scale for Children, fourth edition (WISC-IV); Wechsler Individual Achievement Test, second edition, abbreviated (WIAT-II-A); Beery Developmental Test of Visual Motor Integration; Conners' Continuous Performance Test II (CPT II); and Children's Memory Scale (CMS). Table 2 details the subsets administered and the scores analyzed.

Parents of participants completed a demographic and medical history survey. Parents were asked about their marital status, education, and income. This questionnaire confirmed that the child was developing normally before the ALL diagnosis as an additional check of eligibility for this study. Also, parents were asked about neurologic events, special education services, and psychotropic drug use during and after ALL therapy.

Data Analysis

Characteristics such as age, sex, and therapy history were summarized and were compared between participants and nonparticipants by using *t* test, χ^2 test, and Fisher's exact test to evaluate the potential for response bias. These characteristics also were compared between those randomly assigned to IT methotrexate versus triple IT therapy to determine comparability of exposed groups.

Multiple linear regression was used to evaluate the differences in neurocognitive outcomes between the IT groups, and analysis was adjusted for sex, age at diagnosis, and elapsed time since diagnosis. Adjusted least squares means and standard errors (SEs) for the neurocognitive outcomes, as well as 95% CIs for treatment group differences in the means, are presented. In addition, the proportion of patients with standard scores at or worse than one standard deviation less than the norm was compared by using χ^2 test or Fisher's exact test.

Subgroup analyses also were conducted to determine whether the differences in neurocognitive outcomes between treatment groups were modified by sex and/or age at diagnosis (< 3 years *v* $\geq$ 3 years). Post-hoc analyses were conducted to assess the impact of the formulation of the thiopurine (ie, mercaptopurine *v* thioguanine) on neurocognitive functioning.

The sample size of 82 and 89 patients in the two IT groups provided 80% power at the two-sided .05 significance level to detect a difference of 0.4 standard deviations between the two group means. For example, there was adequate power to detect a difference of six IQ points between groups.

Data were analyzed with the SAS software package, version 9.1 (SAS Institute, Cary, NC), with two-sided tests at the .05 significance level. The data were analyzed by the Biostatistics and Study Design Core of the Yale Center for Clinical Investigation in collaboration with the COG Biostatistics Committee.

RESULTS

Participants

There were 171 participants with neurobehavioral data available for analysis. The participants of this study were similar to the 1,856 patients enrolled on CCG 1952 in terms of sex, age at diagnosis, corticosteroid random assignment, and mercaptopurine random assignment. However, the current sample was more likely to be white (81% *v* 67% in CCG 1952; *P* < .001).

Table 3 lists the characteristics of participants, stratified by IT random assignment. Patients in the different IT treatment groups were similar in terms of sex, elapsed time since diagnosis, ethnicity, education of primary caregiver, and family income. Patients who received IT methotrexate were slightly older at ALL diagnosis (4.6 *v* 4.0

Table 3. Demographic and Clinical Characteristics of Participants Previously Randomly Assigned to IT Methotrexate or Triple IT Therapy

Characteristic	Randomly Assigned Treatment*				P†
	IT Methotrexate (n = 82)		Triple IT Therapy (n = 89)		
	No.	%	No.	%	
Age at diagnosis, years					
Mean		4.6		4.0	.04
SD		2.1		1.8	
Sex					
Female	38	46	39	44	
Male	44	54	50	56	.76
Years between diagnosis and start of the study					
Mean					
SD	5.9	1.0	6.0	1.2	.44
Ethnicity					
White, non-Hispanic	62	79	71	82	
Hispanic	5	6	10	11	
Black, non-Hispanic	2	3	1	1	
Asian	1	1	1	1	
Mixed	8	10	4	5	.48
Marital status of primary caregiver					
Married	71	91	67	78	
Unmarried	7	9	19	22	.03
Education of primary caregiver					
High school or less	18	23	32	37	
Some college	30	39	26	30	
College degree or higher	29	38	29	33	.16
Family income, \$					
< 50,000	18	25	30	36	
50,000-80,000	26	36	28	34	
≥ 80,000	29	40	25	30	.25
Thiopurine secondary random assignment					
Mercaptopurine	34	41	42	47	
Thioguanine	48	59	47	53	.45

NOTE. Some participants declined to report marital status, ethnicity, education, and/or family income.

Abbreviations: IT, intrathecal; SD, standard deviation.

*Overall, 48% of patients were assigned to receive methotrexate; 52% were assigned to receive triple intrathecal therapy.

†By *t* test or χ^2 .

years; $P = .04$) and were more likely to have a married primary caregiver (91% v 78%; $P = .03$).

The thiopurine groups were equally distributed between those randomly assigned to IT methotrexate and triple IT therapy. Post-hoc analyses comparing neurocognitive performance between the mercaptopurine and thioguanine showed no differences for any of the neurocognitive domains (data not shown).

Performance on Neurobehavioral Instruments

Table 4 lists the least squares means of neurocognitive test results among patients randomly assigned to IT methotrexate or to triple IT therapy, as adjusted for sex, age at diagnosis, and elapsed time since diagnosis. Patients who received IT methotrexate scored 3.6 points lower, or about one fourth of a standard deviation, on Processing Speed Index ($P = .04$). Otherwise, the groups performed similarly in tests of full-scale IQ, academic achievement, attention/concentration, memory, and visual motor integration. Caregiver marital status and caregiver education were not significant predictors of neurocognitive functioning for any of the domains tested.

The distribution of scores in the two treatment groups then was examined by comparing the proportion of patients with standardized scores at or worse than one standard deviation less than the norm

(Table 5). For Processing Speed Index, children randomly assigned to IT methotrexate were more likely to score in the below-average range than those who received triple IT therapy (19.5% v 6.9%; $P = .02$). No differences were observed for the other domains of neurocognitive functioning.

Potential interactions were tested. The association of treatment with the different measures of cognitive functioning was not modified by sex or age at diagnosis.

Other Measures of Neurobehavioral Status

The frequency of neurologic events reported during therapy was higher among patients randomly assigned to IT methotrexate (23.1%) than among those who received triple IT therapy (8.1%; $P = .01$), largely because of more reports of loss of limb function and altered mental status. In the post-therapy period, there were no group differences in history of special education services, neurologic events, or use of psychotropic medications (Table 6).

DISCUSSION

In general, there were no significant differences in long-term neurocognitive and academic performance in children with ALL previously

Table 4. Comparison of Neurocognitive Test Scores Between Patients Randomly Assigned to Either IT Methotrexate or Triple IT Therapy

Instrument/Scale by Domain Type	Treatment Group				Analysis		
	IT Methotrexate		Triple IT Therapy		Difference*	95% CI	P
	Mean	SE	Mean	SE			
Intelligence							
WISC-IV							
Full scale IQ	99.2	1.3	99.7	1.3	-0.5	-4.2 to 3.2	.80
Academic achievement							
WIAT-II							
Word reading	101.1	1.3	101.4	1.3	-0.3	-3.9 to 3.3	.86
Numerical operations	100.4	1.7	102.3	1.6	-1.9	-6.5 to 2.7	.42
Spelling	101.9	1.6	101.9	1.5	-0.01	-4.4 to 4.4	1.00
Processing speed							
WISC-IV							
Processing speed index	93.7	1.3	97.3	1.2	-3.6	-7.1 to -0.12	.04
Attention/concentration							
CPT II							
Omissions	47.5	1.0	46.8	0.9	0.7	-1.9 to 3.4	.57
Commissions	49.3	1.3	48.0	1.2	1.3	-2.3 to 4.8	.48
Reaction time	46.9	1.2	47.0	1.2	-0.1	-3.4 to 3.3	.97
Variability T-score	46.7	1.2	45.9	1.1	0.7	-2.6 to 4.1	.66
Memory							
CMS							
Visual immediate index	100.8	1.6	101.9	1.5	-1.1	-5.5 to 3.3	.62
Verbal immediate index	103.2	1.7	102.0	1.6	1.1	-3.4 to 5.7	.61
General memory index	104.6	1.8	105.0	1.7	-0.4	-5.2 to 4.4	.87
Working memory							
WISC-IV							
Working memory	98.6	1.6	97.2	1.6	1.4	-3.0 to 5.8	.52
Visual motor integration							
Visual motor integration	91.3	1.4	93.0	1.4	-1.7	-5.7 to 2.3	.40

NOTE. Data are presented as least squares means from multiple linear regression adjusted for sex, age at diagnosis, and time elapsed since diagnosis.

Abbreviations: IT, intrathecal; SE, standard error; WISC-IV, Wechsler Intelligence Scale for Children, fourth edition; IQ, intelligence quotient; WIAT, Wechsler Individual Achievement Test; CPT II, Conners' Continuous Performance Test II; CMS, Children's Memory Scale.

*Difference in adjusted least mean squares between IT methotrexate and triple IT therapy groups.

Table 5. Proportion of Patients With Neurocognitive Instrument Scores Worse Than One Standard Deviation Less Than the Normative Mean, Stratified by IT Random Assignment

Instrument/Scale by Domain Type*	Treatment Group						P†
	IT Methotrexate			Triple IT Therapy			
	No. of Patients	Total No. of Patients	% of Patients	No. of Patients	Total No. of Patients	% of Patients	
Intelligence							
WISC-IV							
Full-scale IQ	8	82	9.8	8	87	9.2	1.00
Academic achievement							
WIAT-II							
Word reading	5	81	6.2	7	88	8.0	.77
Numerical operations	9	81	11.1	12	88	13.6	.68
Spelling	7	81	8.6	14	88	15.9	.18
Processing speed							
WISC-IV							
Processing speed index	16	82	19.5	6	87	6.9	.02
Attention/concentration							
CPT II							
Omissions	1	71	1.4	0	82	0.0	NA
Commissions	14	71	19.7	19	82	23.2	.72
Reaction time	22	71	31.0	24	82	29.3	.86
Variability T-score	20	71	28.2	27	82	32.9	.60
Memory							
CMS							
Visual immediate index	7	76	9.2	12	86	14.0	.46
Verbal immediate index	7	76	9.2	10	86	11.6	.80
General memory index	5	76	6.6	7	86	8.2	.77
Working memory							
WISC-IV							
Working memory	13	82	15.9	12	87	13.8	.83
Visual motor integration							
Beery							
Visual motor integration	23	82	28.0	22	85	25.9	.86

NOTE. No significant difference was found between characteristics of participants who completed a particular instrument versus those who did not.

Abbreviations: IT, intrathecal; WISC-IV, Wechsler Intelligence Scale for Children, fourth edition; IQ, intelligence quotient; WIAT-II, Wechsler Individual Achievement Test, second edition; CPT II, Conners' Continuous Performance Test II; NA, not applicable; CMS, Children's Memory Scale.

*Some participants did not complete all study instruments. Of note, 18 patients (IT methotrexate, n = 11; triple IT therapy, n = 7) did not complete the CPT II; nine patients (IT methotrexate, n = 6; triple IT therapy, n = 3) did not complete the CMS. Reasons given by participating psychologists related to computer difficulties and scheduling conflicts, not related to patient refusal.

†Comparison between IT methotrexate and triple IT therapy groups.

randomly assigned to IT methotrexate versus triple IT therapy in this multisite, cross-sectional study. The exception was that patients who received IT methotrexate scored slightly worse—about one fourth of a standard deviation worse—on a test of processing speed. The

IT methotrexate group also had a higher proportion of patients with Processing Speed Index scores at or worse than one standard deviation less than the mean (19% v 7%). There was no difference between IT methotrexate and triple IT therapy groups in neurologic

Table 6. Comparison of Neurologic Complaints, Psychotropic Drug Use, and Special Education Services During and After ALL Therapy, Stratified by IT Random Assignment

Service by Time Around Therapy	Treatment Group						<i>P</i>
	IT Methotrexate			Triple IT Therapy			
	No. of Patients	Total No. of Patients	% of Patients	No. of Patients	Total No. of Patients	% of Patients	
During therapy							
Special education	8	78	10.3	3	87	3.5	.12
Neurologic complaints	18	78	23.1	7	87	8.1	.01
After therapy							
Special education	19	78	24.4	23	87	26.4	.86
Neurologic complaints	22	78	28.2	23	87	26.4	.86
Psychotropic medications	12	78	15.4	14	87	16.1	1.00

Abbreviations: ALL, acute lymphoblastic leukemia; IT, intrathecal.

complications, psychotropic drug use, or special education services post-therapy by parent report. A substantial number of patients (approximately 25%), however, received special education services after completing therapy for ALL, which indicated the elevated need for these services in this population. This is the first study, to our knowledge, to compare long-term neurocognitive functioning in ALL patients according to the formulation of IT therapy that they received.

Though the neurocognitive outcomes have not been compared previously, IT medications have long been known to be potentially neurotoxic. Acutely, IT methotrexate and—less so, IT cytarabine—are associated with stroke-like syndromes, myelopathy, encephalopathy, and seizures.^{16,17} The mechanism for methotrexate-associated toxicity is not known. Some hypothesize that methotrexate, by inhibiting dihydrofolate reductase, transiently elevates CNS levels of homocysteine, which in turn results in small-vessel vasculopathy. Other investigators believe methotrexate effects are mediated by disruption of brain amines²⁰ or β -oxidation of fatty acids in the cerebrospinal fluid.²¹ It is unclear if higher cumulative IT methotrexate doses are associated with worse outcomes. In a small study of 21 children, the number of IT methotrexate doses was positively associated with neurocognitive impairment.²² However, in a larger study of 121 patients with ALL, cumulative IT dose did not predict cognitive functioning.²³

Among all children who participated in the randomized, controlled study (N = 1,018), grades 3 to 4 CNS toxicity on therapy, as reported by treating physicians, occurred in 5.8% on IT methotrexate and in 6.7% of those on triple IT therapy.⁸ In our cross-sectional sample, parents of patients reported a higher frequency of acute CNS toxic events of any severity during therapy in the IT methotrexate group. There was no difference between IT groups in this study during the post-therapy period. This study was not designed to explain why there was similar long-term neurocognitive functioning in the two groups. Future studies could potentially explore if hydrocortisone interacts with methotrexate or if the neurotoxicity of cytarabine is limited to the acute treatment period.

The major advantage of this study was that the participants of this report had been enrolled on a randomized, controlled, treatment study. Thus, any potential adjuvant therapy or patient-related confounders that could affect neurocognitive functioning likely would be equally distributed between the treatment groups. Patients who received triple IT therapy were more likely to have an unmarried or less-educated caregiver. However, caregiver marital status and caregiver education were not significant predictors of neurocognitive functioning for any of the domains tested. All participants were similar in terms of National Cancer Index standard risk status and lack of cranial radiation. Chemotherapy exposures were identical except for the thiopurine random assignment. To verify that the thiopurine preparation did not confound the association between corticosteroid and neurocognitive functioning, we did post-hoc analyses to compare neurocognitive performance between the mercaptopurine and thio-guanine groups. We found no differences for any of the neurocognitive domains.

These results must be interpreted in the setting of several limitations. We enrolled only 171 of the eligible, traceable 355 patients at the participating institutions who were offered the study. Therefore, there is a potential for participation bias in terms of factors related to neurocognitive functioning. However, the participants were similar to the nonparticipants in terms of age, sex, elapsed time since diagnosis,

and—most importantly—IT random assignment. The total number of participants was adequate to address clinically important differences, as determined by sample size calculations that were based on the *t* test statistic for two independent samples (see Data Analysis section). The patients in the IT methotrexate group were more likely to have a married primary caregiver and trended toward having more educated primary caregivers. However, we do not believe this led to selection bias, because the worse processing speed was observed in the IT methotrexate group. We acknowledge that the lack of parent and teacher questionnaires in our analysis is a potential limitation. Such reports may identify subjective deficits that are not detected by patient performance instruments but that still can affect quality of life.

We used a cross-sectional study design, so causality between treatment exposure and neurocognitive outcome can be inferred but can not be known with certainty. However, longitudinal, prospective studies are more expensive and are difficult to complete with reasonable sample sizes. Furthermore, they often are not feasible to conduct in patients who are ill and/or receiving intensive therapy. Neuropsychological assessments administered at diagnosis in some longitudinal studies have yielded lower than expected cognitive performance scores.^{24,25} Longitudinal studies also can introduce practice effect if done frequently because of general improvement in performance with repeated testing²⁶; methodologic difficulties can result from changing to test instruments appropriate for older ages and/or newer edition forms.

In conclusion, this study did not show any clinically meaningful differences in cognitive functioning between patients previously randomly assigned to IT methotrexate or triple IT therapy. These results do not support modifying IT therapy for ALL because of differential effects on neurocognitive outcome. A small difference in processing speed was seen between children randomly assigned to triple IT therapy versus IT methotrexate, but is not of a magnitude to support differential follow-up of either group. Therefore, clinicians, teachers, and parents should monitor children treated with any IT therapy for the need for accommodation in this domain. For example, extra time for examinations may be needed. The Children's Oncology Group Long-Term Follow-Up Guidelines (<http://www.survivorshipguidelines.org/>) represent an important resource for evidence- and consensus-based care recommendations for childhood cancer survivors in terms of neurocognitive functioning and overall.²⁷ Our data demonstrated that there is substantial individual variation in neurobehavioral outcome. Detailed investigations of host/drug interactions must be conducted to additionally define the source of this variation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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