original reports

The Impact of Intensified CNS-Directed Therapy on Neurocognitive Outcomes in Survivors of Childhood Acute Lymphoblastic Leukemia Treated Without Cranial Irradiation

Lisa M. Jacola, PhD[1]; Heather M. Conklin, PhD[1]; Kevin R. Krull, PhD[1,2]; Deqing Pei, MS[3]; Cheng Cheng, PhD[3]; Wilburn E. Reddick, PhD[4]; Ching-Hon Pui, MD[5]; and Sima Jeha, MD[5]

abstract

PURPOSE Findings from St Jude Total Therapy Study 16 (Total 16) showed early intensification of triple intrathecal therapy (ITT) improved CNS disease control for children with newly diagnosed acute lymphoblastic leukemia (ALL) at the greatest risk of CNS relapse. We examined the impact of this treatment on end-of-therapy neurocognitive outcomes.

METHODS Between 2007 and 2017, 400 (83.5%) of 479 eligible patients treated with Total 16 risk-directed chemotherapy completed protocol-directed neurocognitive testing at the end of therapy. Intensified ITT was defined as ≥ 21 cumulative doses for patients with low-risk ALL (n = 70/194) and ≥ 27 doses for those with standard-to-high risk ALL (n = 81/206).

RESULTS Compared with age-normative expectations, the overall group had significantly lower estimated intelligence quotient ($P < .0001$), attention ($P = .0051$), working memory ($P = .0001$), processing speed ($P = .0002$), fine motor speed ($P = .0001$), and math ($P = .0087$). Caregiver ratings of patient functioning showed elevated risk for problems in attention ($P = .0173$), executive function ($P = .0001$), and adaptive skills ($P = .0001$). Among the low-risk treatment group, there were no significant differences between patients treated with or without intensified ITT (all P's $> .10$). Among patients with standard-to-high risk ALL, those treated with intensified ITT had poorer working memory ($P = .0328$) and fine motor speed ($P = .0403$), and elevated ratings of inattention ($P = .0189$) and executive dysfunction ($P = .0245$). In the standard-to-high risk group, females treated with intensified ITT had lower working memory scores. Public insurance status was associated with worse neurocognitive outcomes in both treatment groups.

CONCLUSION Standard-to-high risk patients treated with intensified ITT are at moderately increased risk for neurocognitive problems. The findings suggest a threshold effect for ITT exposure, which can inform the design of future clinical trials and approaches to neurocognitive monitoring and intervention.

J Clin Oncol 40:4218-4227. © 2022 by American Society of Clinical Oncology

INTRODUCTION

Acute lymphoblastic leukemia (ALL), the most common childhood malignancy, accounts for about 25% of all childhood cancers.[1] Ten-year survival rates are approximately 90% for children with standard-risk disease treated on contemporary protocols.[2] Treatment modifications, including replacement of cranial radiation therapy with intrathecal chemotherapy for CNS prophylaxis, have resulted in relative preservation of global cognitive function in survivors.[3] Neurocognitive studies in children treated with chemotherapy only show elevated risk for difficulties in attention, processing speed, fine motor coordination, and executive function, including working memory.[4-6] Neurocognitive difficulties emerge during treatment, and predict reduced academic achievement, lower overall educational attainment, and lower quality of life for survivors.[7-9]

Demographic predictors of neurocognitive problems in survivors of childhood ALL include younger age at diagnosis[7,10-13] and female sex.[10,13,14] Recent studies have highlighted the role of low socioeconomic status as a predictor of poorer neurocognitive outcomes.[15,16] The association between higher intensity of CNS-directed therapy and neurocognitive impairment has been documented in studies comparing outcomes by treatment risk arm[3,8] and in studies investigating the effects of higher cumulative methotrexate exposure.[10,17]

The St Jude Total Therapy 16 clinical trial (Total 16) evaluated whether a higher dosage of PEG-asparaginase and early intensification of triple intrathecal therapy (ITT; methotrexate, hydrocortisone, and cytarabine) would improve systemic and CNS control in children with newly diagnosed ALL.[18] The 5-year event-free and overall survival rates were 88.2% and 94.1%, respectively. Intensified ITT during early

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on September 19, 2022 and published at ascopubs.org/journal/jco on November 2, 2022: DOI https://doi.org/10.1200/JCO.22.00263

CONTEXT

Key Objective

To examine the impact of intensified triple intrathecal therapy (ITT) on neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia treated on the St Jude Total Therapy 16 study.

Knowledge Generated

Three years after diagnosis, a significant proportion of the overall group of survivors showed elevated neurocognitive risk. Among patients treated with standard-to-high risk therapy, compared with those receiving lower cumulative ITT doses, patients treated with intensified ITT had worse neurocognitive outcomes. No impact of intensified ITT was evident among patients treated on the low-risk arm.

Relevance *(S. Bhatia)*

This study identifies a threshold dose effect for the association between intrathecal therapy and cognitive impairment. This finding can inform future intervention strategies to mitigate the risk.*

*Relevance section written by *JCO* Associate Editor Smita Bhatia, MD, MPH.

remission induction improved CNS control compared with historical controls treated on St Jude Total Therapy 15.[19] Among patients at elevated risk for CNS relapse, the 5-year rate of any CNS relapse of 1.8% was significantly lower than that of patients with similar risk treated on the Total 15 study (5.7%). The intensified ITT during early remission induction was not associated with elevated cumulative risk of acute neurotoxicity. We extend these findings by examining the impact of intensified ITT on neurocognitive outcomes, using data obtained from protocol-driven neurocognitive testing completed at the end of treatment. We hypothesized that intensified ITT would be associated with more neurocognitive impairment.

METHODS

Participants

A total of 598 patients age 0-18 years at diagnosis received risk-directed chemotherapy on Total 16 between 2007 and 2017. Of these, 479 (80.1%) were eligible for neurocognitive monitoring (Appendix Fig A1, online only). Reasons for ineligibility were Down syndrome (n = 12), English not primary language (n = 25), removal from treatment before the end of therapy (n = 54), and lack of consent (n = 28).

End-of-therapy neurocognitive testing was obtained for 400 of 479 eligible patients (83.5%; Table 1). The majority of patients were White (80.4%), non-Hispanic (93.3%), and male (58.8%). Consistent with the approach taken in previous studies, insurance type was used as a proxy for socioeconomic status (private = 52.5%, public or none = 47.5%).[15,16] The mean age at diagnosis was 7.05 years (standard deviation [SD] = 4.63), the mean cumulative frequency of ITT was 19.58 (SD = 5.64), and the mean age at testing was 9.67 years (SD = 4.65).

Protocol-Directed Treatment

Treatment details and primary outcomes for Total 16 have been previously reported.[18] Patients were classified as having low-risk, standard-risk (intermediate-risk), or high-risk leukemia on the basis of presenting characteristics and early response to treatment. Remission induction consisted of prednisone, vincristine, daunorubicin, and PEG-asparaginase, followed by cyclophosphamide, cytarabine, and a thiopurine. All patients received four courses of high-dose methotrexate and mercaptopurine as consolidation treatment followed by antimetabolite-based continuation therapy, including two cycles of reinduction therapy. During the first 2 years of continuation therapy, all patients received pulses of dexamethasone and vincristine every 4 weeks (low-risk, 8 mg/m^2 per day; standard-to-high risk 12 mg/m^2/d). Patients were randomly assigned to receive PEG-asparaginase 3,500 U/m^2 versus the conventional 2,500 U/m^2 on the first day of continuation treatment. Standard-to-high risk patients received additional PEG-asparaginase every 2 weeks interrupted with pulses of doxorubicin during the first 20 weeks of continuation treatment, followed by three rotating drug pairs. The total duration of continuation therapy was 120 weeks for both males and females. No patients received prophylactic cranial radiation therapy.

CNS-Directed Therapy

ITT was administered during all phases of therapy at an age-appropriate dose, and the total number of doses varied according to presenting characteristics and CNS status.[18] Patients treated on the low-risk arm were prescribed 13, 19, or 21 doses. Patients treated on the standard-to-high risk arm were prescribed 16, 25, or 27 doses. Patients at the greatest risk for CNS relapse were prescribed the highest dose level in both arms (low-risk = 21, standard-to-high risk = 27). We aimed to investigate the association of intensified CNS-directed therapy with neurocognitive

TABLE 1. Demographic and Clinical Characteristics for Patients Completing Neurocognitive Testing

Demographic and Clinical Characteristics	Overall Group (N = 400)	Low-Risk (n = 194)	Standard-to-High Risk (n = 206)
Sex, No. (%)			
Female	165 (41.3)	87 (44.8)	78 (37.9)
Male	235 (58.8)	107 (55.2)	128 (62.1)
Race, No. (%)			
White	320 (80.4)	159 (82.4)	161 (78.5)
Black	55 (13.8)	22 (11.4)	33 (16.1)
Multiracial	14 (3.5)	8 (4.1)	6 (2.9)
Asian	9 (2.3)	4 (2.1)	5 (2.4)
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, No. (%)			
Hispanic	25 (6.3)	11 (5.7)	14 (6.9)
Not Hispanic	373 (93.3)	183 (94.3)	190 (93.1)
Insurance type, No. (%)			
Private	210 (52.5)	105 (54.1)	105 (51.0)
Public or none	190 (47.5)	89 (45.9)	101 (49.0)

Demographic and Clinical Characteristics	Mean	SD	Mean	SD	Mean	SD
Age at diagnosis, years	7.05	4.63	5.08	2.99	8.90	5.13
Age at assessment, years	9.67	4.65	7.67	2.98	11.53	5.13
Cumulative ITT frequency	19.58	5.64	15.99	3.89	22.96	4.91

NOTE. Race is missing for two participants.

Abbreviations: ITT, triple intrathecal therapy; SD, standard deviation.

outcomes; as such, ITT frequency was used as a categorical variable within groups on the basis of treatment arm: low-risk ≤ 20 or ≥ 21 doses and standard-to-high risk ≤ 26 or ≥ 27 doses (Appendix Table A1, online only). Systemic therapy was not further intensified specifically for patients with highest CNS risk within the separate treatment arms.

Neurocognitive Assessment

Eligible and consented patients completed neurocognitive assessment at continuation week 120 (end of therapy), about 3 years after diagnosis. Measures were administered by psychologic examiners under supervision of a licensed clinical psychologist. The assessment included standardized performance measures and caregiver ratings with demonstrated reliability and validity (Appendix Table A2, online only). Patients completed age-appropriate measures of estimated global intelligence,[20] sustained attention,[21,22] working memory,[23-26] processing speed and executive function,[23] verbal learning and memory,[27,28] fine motor speed,[29] and academics.[30] Caregivers completed ratings of the patient's attention,[31] executive function,[32,33] and adaptive skills.[34] Written informed consent, with assent from the patient as appropriate, was obtained before assessment. The neurocognitive study was embedded in Total 16, which was approved by the Institutional Review Board at St Jude Children's Research Hospital.

Statistical Analyses

Variables abstracted from the clinical trial database included sex, race, ethnicity, age at diagnosis, treatment risk arm, and cumulative frequency of ITT. Insurance type was abstracted from the medical record. Descriptive statistics were calculated for patient sex, race, ethnicity, insurance status, age at diagnosis, and cumulative frequency of ITT. Frequency or mean comparisons (chi-square or two-sample *t* test) were performed to compare eligible and ineligible participants.

Descriptive statistics, including mean, standard deviation, and percent at elevated risk, were calculated for all neurocognitive outcomes in the overall group. Elevated risk was defined as ≥ 1 SD outside the mean of the normative sample. One-sample *t* tests were performed to compare the group mean scores to normative expectations. Chi-square tests were performed to compare frequency of elevated risk scores to normative expectations (16th percentile). For these analyses, two-sided *P* values were false discovery rate–corrected for multiple comparisons by cognitive domain. We selected outcomes for subsequent analyses on the basis of these findings and in consideration of vulnerable neurocognitive domains in survivors of childhood ALL identified in existing literature.

Univariate analysis of variance was performed to examine the association of predictor variables with neurocognitive outcomes. Stratified analyses were performed for low and standard-to-high treatment risk groups. Predictor variables were patient sex, insurance type (private; public or none), and ITT frequency (low-risk ≤ 20 or ≥ 21, standard-to-high risk ≤ 26 or ≥ 27 doses). Bivariate correlations were used to examine the association of age at diagnosis with neurocognitive outcomes, with separate analyses performed for treatment risk groups. For outcomes where multiple predictors were significant in univariate analysis, the general linear model was used to test for interactions.

In an exploratory analysis, we compared learning and memory between patients treated on Total 15 or 16 with presenting features associated with increased risk for CNS relapse. Additional exploratory case-control analyses examined the association of acute neurotoxicity and severe infection with neurocognitive outcomes.

All tests of statistical significance were two-sided. Standardized scores from neurocognitive tests were transformed into *Z* scores (mean = 0, SD = 1.0) for ease of

TABLE 2. Neurocognitive Outcomes at the End of Therapy for the Overall Group

Neurocognitive Outcomes	Mean	SD	P^a	Elevated Risk, %	P^b
Global intelligence					
Estimated IQ	–0.20	0.97	**< .0001**	17.0	.7010
Attention					
Omissions	0.56	2.16	**.0002**	22.4	**.0479**
Hit Reaction Time	–0.18	1.15	**.0051**	26.3	.7501
Variability	0.54	1.09	**.0002**	34.5	**< .0001**
Detectability	0.27	1.00	**.0002**	24.2	**.0216**
Beta	0.05	0.97	.2935	10.0	**.0446**
Attention Problems[c]	0.13	1.01	**.0173**	20.8	.1231
Working memory					
Auditory Working Memory	0.20	0.86	**.0001**	6.7	**.0001**
Digit Span	–0.49	0.93	**.0001**	34.4	**< .0001**
Processing speed					
Visual Matching	–0.34	1.07	**.0002**	21.5	.0996
Decision Speed	0.03	1.12	.5500	16.2	.9190
Executive function					
Retrieval Fluency	–0.27	0.89	**.0001**	19.1	.2465
Global Executive[c]	0.28	1.16	**.0001**	27.2	**.0210**
Learning and memory					
List A Total	–0.03	0.98	.6092	18.0	.4700
Short Delay Free Recall	–0.07	1.02	.2966	23.7	**.0192**
Long Delay Free Recall	–0.08	1.09	.2966	22.5	**.0381**
Learn Slope	–0.15	1.00	**.0306**	25.2	**.0150**
Discriminability	0.11	1.24	.2966	15.6	**.0192**
Fine motor					
Purdue Pegs	–0.62	1.18	**.0001**	38.7	**< .0001**
Academics					
Letter Word Identification	–0.08	0.98	.2046	16.8	.8355
Spelling	–0.04	0.97	.4161	16.9	.8355
Applied Problems	–0.14	0.85	**.0087**	15.3	.8355
Adaptive skills					
Global Adaptive[c]	–0.29	1.10	**.0001**	23.7	**.0105**

NOTE. N = 400. *Z* score normative mean = 0, SD = 1. Bold values indicate results significant at $P < .05$, false discovery rate corrected for multiple comparisons by neurocognitive domain.

Abbreviations: IQ, intelligence quotient; SD, standard deviation.

[a]Two-sided *P* value from one-sample *t* test comparing group means to normative expectations.

[b]Two-sided *P* value from chi-square comparing elevated risk score frequency to normative expectations (16th percentile).

[c]Caregiver ratings.

presentation. Data were analyzed using SAS Version 9.3 and IBM SPSS Statistics 25.

RESULTS

There was no significant difference between eligible and ineligible groups by sex ($P = .6250$) or age at diagnosis ($P = .3459$; Appendix Table A3 [online only]). Compared with eligible patients, ineligible patients, including those who were removed from treatment before the end of therapy, had lower cumulative ITT (mean total dose = 19.18 and 16.28, respectively, $P < .0001$). The distribution of insurance type differed between groups, with a greater percentage of ineligible patients having public or no insurance (50.7% and 64.7%, respectively, $P = .0062$).

See Table 2 for neurocognitive outcomes for the overall group. Mean scores were below age-based norms on measures of global intelligence (Estimated intelligence quotient [IQ], $P < .0001$), attention (Omissions, $P = .0002$; Hit Reaction Time, $P = .0051$; Variability, $P = .0002$; Detectability, $P = .0002$), working memory (Auditory Working Memory, $P = .0001$; Digit Span, $P = .0001$), processing speed (Visual Matching, $P = .0002$), executive function (Retrieval Fluency, $P = .0001$), rate of new memory formation (Learn Slope, $P = .0306$), fine motor speed (Purdue Pegs, $P = .0001$), and math (Applied Problems, $P = .0087$). Compared with normative expectations, caregivers rated patients as having greater problems with attention ($P = .0173$) and executive function (Global Executive, $P = .0001$), and less independence with activities of daily living (Global Adaptive, $P = .0001$). Compared with low-risk patients, standard-to-high risk patients had worse performance in working memory (Auditory Working Memory, $P = .0070$), processing speed (Visual Matching, $P = .0040$), and math (Applied Problems, $P = .0465$; Appendix Table A4 [online only]).

Table 3 presents the results from univariate analyses examining associations of sex and insurance type with neurocognitive outcomes by treatment risk arm. Among low-risk patients, males performed worse than females on measures of global intelligence (Estimated IQ, $P = .0016$), processing speed (Visual Matching, $P = .0067$), executive function (Retrieval Fluency, $P = .0135$), and fine motor speed (Purdue Pegs, $P = .0117$), and had higher ratings of executive dysfunction (Global Executive, $P = .0089$) and adaptive independence (Global Adaptive, $P < .0001$). Among low-risk patients, compared with the cohort with private insurance, the cohort with public or no insurance had lower global intelligence (Estimated IQ, $P = .0012$), processing speed (Visual Matching, $P = .0250$), and math achievement (Applied Problems, $P = .0084$), and higher ratings of inattention (Attention Problems, $P = .0026$) and executive dysfunction (Global Executive, $P = .0025$). Among standard-to-high risk, males had lower performance in working memory (Digit Span, $P = .0026$) and processing speed (Visual Matching, $P = .0041$) compared with females. Compared with standard-to-high risk patients with private insurance, those with public or no insurance performed worse in processing speed (Visual Matching, $P = .0204$) and math (Applied Problems, $P = .0029$).

The association of age at diagnosis and neurocognitive outcomes varied by treatment risk arm. There were no significant associations between age at diagnosis and neurocognitive

TABLE 3. Univariate Association of Sex and Insurance Type With Neurocognitive Outcomes by Treatment Risk Arm

	Sex					Insurance Type				
	Female		Male			Private		Public or None		
Neurocognitive Outcomes	Mean	SD	Mean	SD	*P*[a]	Mean	SD	Mean	SD	*P*[b]
Low-risk										
Global intelligence										
Estimated IQ	0.00	0.90	–0.47	1.09	**.0016**	–0.04	1.01	–0.53	1.01	**.0012**
Attention										
Omissions	0.47	1.26	0.35	1.32	.5686	0.24	1.07	0.61	1.51	.0691
Attention Problems[c]	0.02	0.96	0.21	1.03	.1941	–0.08	0.96	0.36	1.00	**.0026**
Working memory										
Digit Span	–0.42	0.87	–0.70	0.83	.0760	–0.40	0.76	–0.79	0.92	.0121
Processing speed										
Visual Matching	0.06	0.83	–0.35	1.11	**.0067**	–0.01	1.03	–0.35	0.96	**.0250**
Executive function										
Retrieval Fluency	–0.11	0.77	–0.44	0.93	**.0135**	–0.19	0.88	–0.41	0.86	.1031
Global Executive[c]	0.00	1.07	0.44	1.14	**.0089**	0.01	1.06	0.52	1.14	**.0025**
Learning and memory										
Learning Slope	–0.07	0.92	–0.24	1.09	.3050	–0.14	0.94	–0.19	1.11	.7393
Fine motor										
Purdue Pegs	–0.31	1.05	–0.72	1.11	**.0117**	–0.45	1.10	–0.64	1.10	.2493
Academics										
Applied Problems	0.05	0.80	–0.09	0.91	.2865	0.14	0.87	–0.21	0.83	**.0084**
Adaptive skills										
Global Adaptive[c]	0.11	1.01	–0.55	1.00	**< .0001**	–0.12	1.04	–0.42	1.06	.0682
Standard-to-high risk										
Global intelligence										
Estimated IQ	–0.04	0.82	–0.21	0.93	.1841	–0.04	0.79	–0.25	0.97	.1043
Attention										
Omissions	0.93	3.65	0.55	1.92	.3529	0.82	3.26	0.57	1.95	.5405
Attention Problems[c]	0.17	0.93	0.12	1.07	.7648	0.08	1.05	0.20	0.98	.4694
Working memory										
Digit Span	–0.11	0.78	–0.59	1.04	**.0026**	–0.38	0.87	–0.47	1.06	.5553
Processing speed										
Visual Matching	–0.22	1.10	–0.68	1.06	**.0041**	–0.31	1.07	–0.67	1.08	**.0204**
Executive function										
Retrieval Fluency	–0.13	0.92	–0.32	0.91	.1537	–0.17	0.87	–0.30	0.95	.3060
Global Executive[c]	0.17	1.06	0.41	1.27	.1874	0.30	1.14	0.33	1.26	.8620
Learning and memory										
Learning Slope	0.02	1.07	–0.25	0.93	.0906	–0.07	1.01	–0.24	0.97	.2738
Fine motor										
Purdue Pegs	–0.50	1.10	–0.82	1.30	.0758	–0.60	1.18	–0.79	1.24	.2540
Academics										
Applied Problems	–0.19	0.88	–0.27	0.80	.4844	–0.06	0.78	–0.42	0.84	**.0029**
Adaptive skills										
Global Adaptive[c]	–0.24	1.18	–0.37	1.13	.4524	–0.26	1.14	–0.40	1.15	.4055

NOTE. Bold values indicate results significant at $P < .05$.

Abbreviations: IQ, intelligence quotient; SD, standard deviation.

[a]Two-sided *P* value from one-way analysis of variance comparing outcomes by patient sex.

[b]Two-sided *P* value from one-way analysis of variance comparing outcomes by patient sex.

[c]Caregiver ratings. The results are presented in *Z* scores, with a normative mean of 0 and SD of 1.

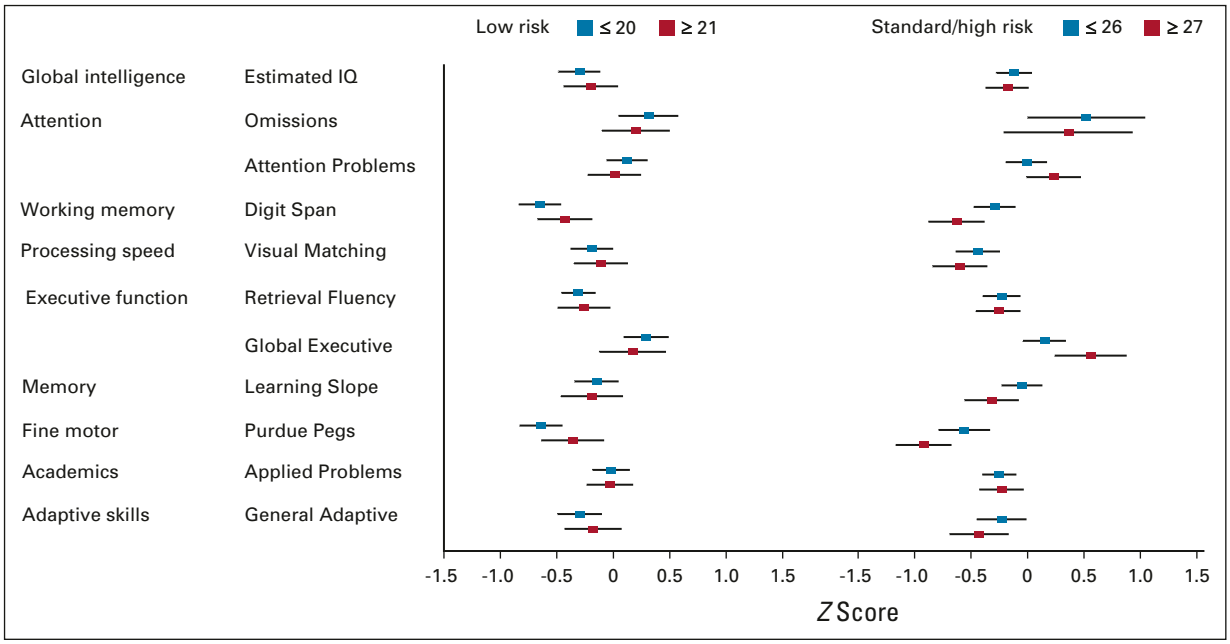

FIG 1. Association of ITT frequency with neurocognitive outcomes by treatment risk arm. [a]Caregiver ratings. *Z* score normative mean = 0, SD = 1. Two-sided *P* values from one-way ANOVA by ITT frequency group in low and standard-to-high treatment risk groups. For each measure, a mean that falls outside of the 95% CI of the other mean is significantly different from the second mean at $P < .05$. ANOVA, analysis of variance; ITT, triple intrathecal therapy; IQ, intelligence quotient; SD, standard deviation.

outcomes in patients treated with low-risk therapy. For standard-to-high risk patients, younger age at diagnosis predicted slower verbal retrieval, as aspect of executive function (Retrieval Fluency, $r = 0.15$, $P = .0352$), greater adaptive independence ($r = 0.17$, $P = .0283$), and worse math performance (Applied Problems, $r = –0.21$, $P = .0044$).

Figure 1 presents the results of univariate associations of ITT frequency and neurocognitive outcomes by treatment risk group. There were no significant associations between ITT frequency and neurocognitive outcomes in the low-risk group. Among standard-to-high risk patients, those treated with ≥ 27 ITT doses had lower scores in working memory (Digit Span, $P = .0328$) and slower fine motor speed (Purdue Pegs, $P = .0403$), and elevated ratings of inattention ($P = .0190$) and executive dysfunction ($P = .0245$) than patients treated with ≤ 26 ITT doses. Among standard-to-high risk patients treated with intensified ITT, elevated risk for neurocognitive impairment was evident across domains, and most prominent in working memory (43.1%), fine motor (52.5%), and learning/memory (29.7%; Fig 2).

Among the standard-to-high risk treatment group, patient sex moderated the relationship between ITT frequency and working memory ($P = .0019$). Males had lower scores than females in both ITT frequency groups, but the difference was significant in the lower dose group only (mean [SD], ≤ 26 doses: males = –0.52 [1.00], females = 0.09 [0.76], $P = .0015$; ≥ 27 doses, males = –0.70 [1.10], females = –0.50 [0.67], $P = .4586$; Fig 3). Among females, those treated with ≤ 26 ITT doses had higher scores than those treated with ≥ 27 doses ($P = .0053$).

An exploratory analysis showed no significant differences in neurocognitive outcomes between patients with presenting features associated with elevated CNS relapse risk on Total 15 or 16 (List A Total, $P = .5322$; Short Delay Free Recall, $P = .4283$; Long Delay Free Recall, $P = .5127$; Learn Slope, $P = .4505$; Discriminability, $P = .1026$; Appendix Fig A2 [online only]).

The results from a case-control analysis examining neurocognitive outcomes by acute neurotoxicity status showed patients experiencing seizures had worse performance in math than controls ($P = .0095$; Appendix Table A5 [online only]). The findings from a case-control analysis of neurocognitive outcomes by severe infection status showed no significant differences between groups (Appendix Table A6, online only).

DISCUSSION

Among patients treated with standard-to-high risk therapy, those receiving higher cumulative doses of ITT had working memory and fine motor speed scores lower than patients treated with lower cumulative doses. Patients in the standard-to-high risk arm treated with greater-intensity CNS-directed therapy additionally had elevated risk for inattention and executive dysfunction according to caregiver ratings, illustrating the functional impact of these difficulties in daily life. By contrast, no impact of intensified CNS-directed therapy was evident among patients treated on the low-risk arm. This may suggest a threshold for ITT, with/without systemic therapy, affecting neurocognitive function.

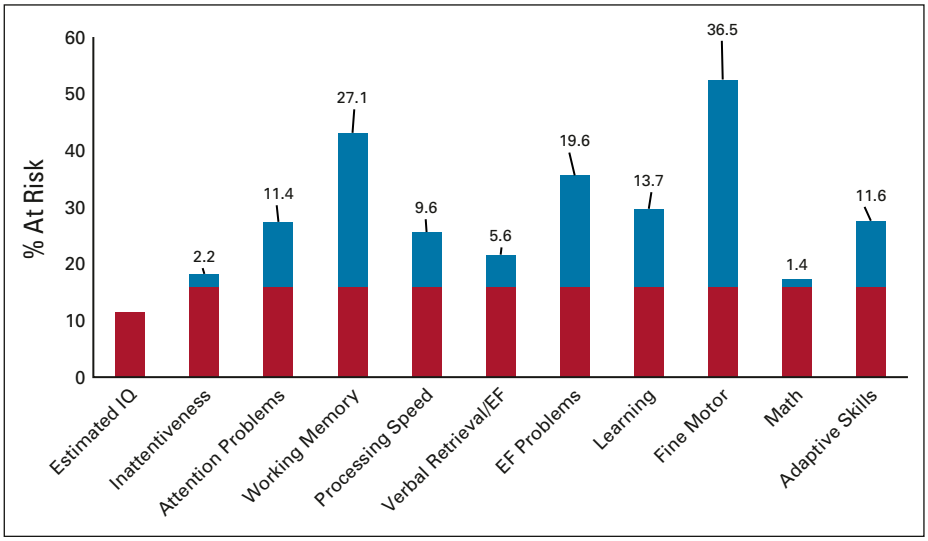

FIG 2. Frequency of elevated neurocognitive risk in patients treated with standard-to-high risk therapy and intensified intrathecal therapy. Elevated risk = scores > 1 SD outside of the mean. Expected value = 16th percentile in the normative population. Blue shading and associated percent values = frequency of patients with at-risk scores. EF, executive function; IQ, intelligence quotient; SD, standard deviation.

The adverse impact of increased methotrexate exposure on neurocognitive outcomes in survivors of childhood ALL treated with chemotherapy-only approaches is well documented, with evidence showing increased intensity of intrathecal and systemic methotrexate increases risk.[5] Our analysis was stratified by treatment risk arm to facilitate comparisons of outcomes by protocol-directed variations in intrathecal cumulative dose by holding other aspects of treatment constant (including high-dose methotrexate).

Among standard-to-high risk patients, males had lower working memory scores than females, although this difference was only significant at the lowest ITT dose. Interestingly, there was evidence for a dose effect among females: patients treated with intensified ITT (≥ 27 doses) had significantly lower working memory scores than those treated with lower ITT doses. These findings seem to be most consistent with a growing body of evidence suggesting that treatment-related neurocognitive impairment and related mechanisms may be sex-specific, with each sex demonstrating a specific neurocognitive risk profile.[35]

We found that 3 years after diagnosis, a significant proportion of the overall group of survivors showed elevated risk for problems in attention, working memory, learning and memory, and fine motor coordination. The results from caregiver ratings showed elevated risk for problems with attention, executive function, and adaptive independence. Regardless of treatment approach, survivors of childhood ALL treated with chemotherapy only have elevated risk for neurocognitive problems. These findings also highlight the complexity of neurocognitive outcomes and the need for research into non–treatment-related neurocognitive risk factors.

As an example, we found a significant effect of insurance type on neurocognitive risk. Compared with those with private insurance, patients with public insurance or no insurance had significantly lower Estimated IQ, working memory, processing speed, and math. These findings are consistent with recent studies of neurocognitive and academic outcomes in children treated for NCI high-risk B-ALL on the Children's Oncology Group frontline therapy trial, AALL0232.[15,16] Multiple studies in the general childhood population have identified an association between low social economic status and alterations in brain structure and function.[36,37] Future work is needed to examine the role of social economic status on the association between treatment-related alterations in brain development and neurocognitive outcomes. Such work would benefit from detailed measurement of environmental constructs known to affect neurocognitive development in the general childhood population, including the role of childhood adverse experiences on brain and cognitive development.[37] Other approaches could consider a broader approach to measurement of social economic status, with the goal of measuring community level factors (eg, access to nutrition, availability of resources, and level of pollution).

We found that younger age at diagnosis predicted neurocognitive problems in patients treated with standard-to-high risk therapy only. Patients in the low-risk treatment group tend to be younger because young children are more likely than older children to have favorable genetic subtypes of ALL and thus generally receive lower intensity of treatment. However, young children with standard-to-high risk leukemia were treated with more intensive chemotherapy,

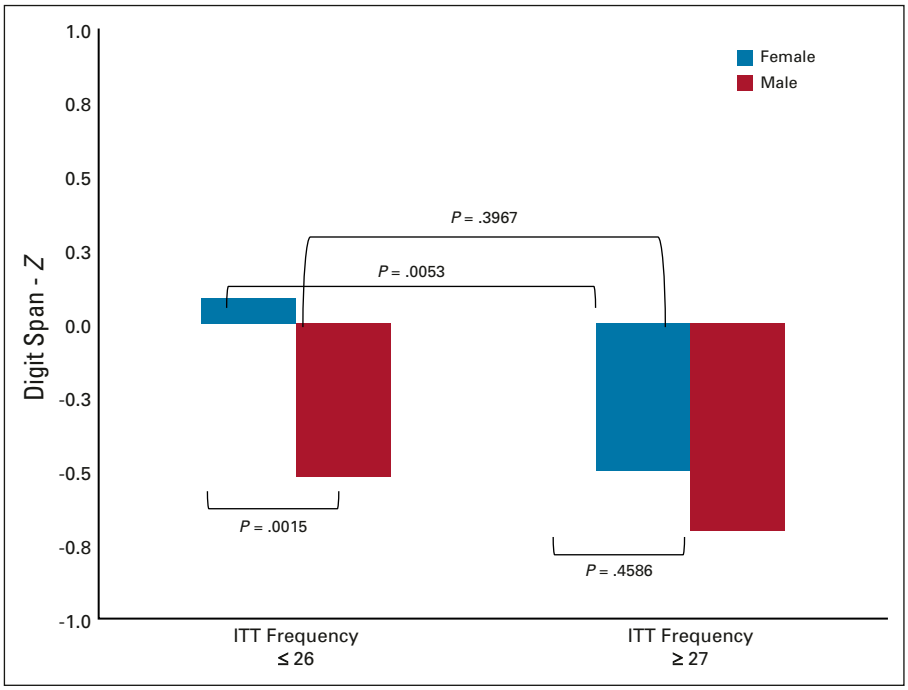

FIG 3. Influence of patient sex on the association between ITT frequency and working memory in the standard-high risk treatment group. Two-sided *P* values from *t* test comparing outcomes by patient sex in each ITT frequency group. ITT, triple intrathecal therapy.

including higher dosages of dexamethasone, a corticosteroid that has been associated in adverse neurodevelopmental impact.[38] Higher intensity of overall treatment may lead to increased need for hospitalization for treatment-related toxicity, leading to decreased opportunities for socialization and learning in the normative environment. Younger age at diagnosis is also a neurocognitive risk factor because of the rapid neurodevelopment of mechanisms that support cognition.[39]

The clinical implications of these findings are significant. Neurocognitive impairment is more likely with higher numbers of intensified ITT. Our large and representative sample is novel and speaks to generalizability of findings. Our findings suggest a threshold effect for exposure to ITT, which can inform future clinical trials and planning, as well as neurocognitive monitoring and preventative interventions during therapy and in survivorship.

Attention and working memory account for nearly half of the developmental gains in global outcomes,[40] and neuroimaging studies in survivors of childhood ALL show that attention and working memory are markers of CNS-directed therapy on brain development.[41,42] As such, neurocognitive vulnerabilities in these foundational domains may critically alter neurodevelopmental trajectory and the development of global intelligence and adaptive skills.

Strengths of this study include prospectively obtained data obtained at a protocol-defined time point. The majority of eligible patients completed neurocognitive testing at 3 years after diagnosis. The test battery was comprehensive and included reliable and valid measures of neurocognitive functioning for patients of all ages, which is particularly important, given the high proportion of very young children diagnosed with ALL. Our study is not without limitations. Patients were treated at a single site. Data are cross-sectional. A greater proportion of patients who were ineligible for neurocognitive monitoring had public or no insurance, suggesting a lower social economic status.

Our results have implications for risk-directed neurocognitive screening and development of interventions to remediate neurocognitive deficits in survivors of childhood ALL. The Psychosocial Standards of Care Project for Childhood Cancer guidelines recommend neurocognitive monitoring beginning during therapy and continuing into survivorship for all patients treated with CNS-directed therapies.[43] However, operationalizing this recommendation is challenging in centers with varying levels of resources, and not all survivors may need comprehensive evaluation. Our findings can be used to inform risk-directed neurocognitive screening and intervention that is feasible across settings, thus promoting evidence-based care for patients and families.[44]

AFFILIATIONS

[1]Department of Psychology, St Jude Children's Research Hospital, Memphis, TN
[2]Department of Epidemiology & Cancer Control, St Jude Children's Research Hospital, Memphis, TN
[3]Department of Biostatistics, St Jude Children's Research Hospital, Memphis, TN
[4]Department of Diagnostic Imaging, St Jude Children's Research Hospital, Memphis, TN
[5]Department of Oncology, St Jude Children's Research Hospital, Memphis, TN

CORRESPONDING AUTHOR

Lisa M. Jacola, PhD, Department of Psychology, St Jude Children's Research Hospital, 262 Danny Thomas Place, Mail Stop 470, Memphis, TN 38105-3678; Twitter: @drlisajacola; e-mail: lisa.jacola@stjude.org.

PRIOR PRESENTATION

Presented at the 2019 International Neuropsychological Society Annual Meeting, New York, NY, February 20-23, 2019.

SUPPORT

Supported by the National Cancer Institute (P30 CA21765 and GM92666 to St Jude Children's Research Hospital, R01 CA90246 to W.E.R.) and the American Lebanese Syrian Associated Charities (ALSAC).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.00263.

AUTHOR CONTRIBUTIONS

Conception and design: Lisa M. Jacola, Heather M. Conklin, Kevin R. Krull, Cheng Cheng, Wilburn E. Reddick, Ching-Hon Pui, Sima Jeha
Provision of study materials or patients: Ching-Hon Pui, Sima Jeha
Collection and assembly of data: Lisa M. Jacola, Heather M. Conklin, Ching-Hon Pui
Data analysis and interpretation: Lisa M. Jacola, Heather M. Conklin, Kevin R. Krull, Deqing Pei, Cheng Cheng
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. American Cancer Society: Cancer Facts & Figures, 2021. https://www.cancer.org/cancer/cancer-in-children/key-statistics.html#references
2. Pui CH, Evans WE: A 50-year journey to cure childhood acute lymphoblastic leukemia. Semin Hematol 50:185-196, 2013
3. Conklin HM, Krull KR, Reddick WE, et al: Cognitive outcomes following contemporary treatment without cranial irradiation for childhood acute lymphoblastic leukemia. J Natl Cancer Inst 104:1386-1395, 2012
4. Krull KR, Brinkman TM, Li C, et al: Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: A report from the St. Jude Lifetime Cohort Study. J Clin Oncol 31:4407-4415, 2013
5. van der Plas E, Modi AJ, Li CK, et al: Cognitive impairment in survivors of pediatric acute lymphoblastic leukemia treated with chemotherapy only. J Clin Oncol 39:1705-1717, 2021
6. Lofstad GE, Reinfjell T, Weider S, et al: Neurocognitive outcome and compensating possibilities in children and adolescents treated for acute lymphoblastic leukemia with chemotherapy only. Front Psychol 10:1027, 2019
7. Jacola LM, Krull KR, Pui CH, et al: Longitudinal assessment of neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia treated on a contemporary chemotherapy protocol. J Clin Oncol 34:1239-1247, 2016
8. Jacola LM, Edelstein K, Liu W, et al: Cognitive, behaviour, and academic functioning in adolescent and young adult survivors of childhood acute lymphoblastic leukaemia: A report from the Childhood Cancer Survivor Study. Lancet Psychiatry 3:965-972, 2016
9. Kunin-Batson A, Kadan-Lottick N, Neglia JP: The contribution of neurocognitive functioning to quality of life after childhood acute lymphoblastic leukemia. Psychooncol 23:692-699, 2014
10. Sherief LM, Sanad R, ElHaddad A, et al: A cross-sectional study of two chemotherapy protocols on long term neurocognitive functions in Egyptian children surviving acute lymphoblastic leukemia. Curr Pediatr Rev 14:253-260, 2018
11. Sleurs C, Lemiere J, Vercruysse T, et al: Intellectual development of childhood ALL patients: A multicenter longitudinal study. Psychooncol 26:508-514, 2017
12. Jansen NCAJ, Kingma A, Schuitema A, et al: Neuropsychological outcome in chemotherapy-only-treated children with acute lymphoblastic leukemia. J Clin Oncol 26:3025-3030, 2008
13. von der Weid N, Moslmann I, Hirt A, et al: Intellectual outcome in children and adolescents with acute lymphoblastic leukaemia treated with chemotherapy alone: Age- and sex-related differences. Eur J Cancer 39:359-365, 2003
14. Cheung YT, Brinkman TM, Mulrooney DA, et al: Impact of sleep, fatigue, and systemic inflammation on neurocognitive and behavioral outcomes in long-term survivors of childhood acute lymphoblastic leukemia. Cancer 123:3410-3419, 2017
15. Hardy KK, Embry L, Kairalla JA, et al: Neurocognitive functioning of children treated for high-risk b-acute lymphoblastic leukemia randomly assigned to different methotrexate and corticosteroid treatment strategies: A report from the Children's Oncology Group. J Clin Oncol 35:2700-2707, 2017
16. Jacola LM, Baran J, Noll RB, et al: Adaptive functioning and academic achievement in survivors of childhood acute lymphoblastic leukemia: A report from the Children's Oncology Group. Pediatr Blood Cancer 68:e28913, 2021
17. Liu W, Cheung YT, Conklin HM, et al: Evolution of neurocognitive function in long-term survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. J Cancer Surviv Res Pract 12:398-406, 2018
18. Jeha S, Pei D, Choi J, et al: Improved CNS control of childhood acute lymphoblastic leukemia without cranial irradiation: St Jude Total Therapy Study 16. J Clin Oncol 37:3377-3391, 2019
19. Pui CH, Campana D, Pei D, et al: Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med 360:2730-2741, 2009
20. Roid G: Stanford-Binet Intelligence Scales (ed 4). Itasca, IL, Riverside Publishing, 2003
21. Conners CK: Conners Kiddie Continuous Performance Test (ed 2). North Tonawanda, NY, Multi-Health Systems, 2001
22. Conners CK: Conners' Continuous Performance Test (CPT II v. 5) (ed 2). North Tonawanda, NY, Multi-Health Systems, 2000
23. Mather N, Woodcock R: Woodcock-Johnson Third Edition, Tests of Cognitive Abilities. Itasca, IL, Riverside Publishing, 2001
24. Wechsler D: Wechsler Intelligence Scale for Children (ed 4). Palm Beach Gardens, FL, Pearson Psychological Corporation, 2004

25. Wechsler D: Wechsler Preschool and Primary Scales of Intelligence (ed 3). Palm Beach Gardens, FL, Pearson Psychological Corporation, 2002
26. Wechsler D: Wechsler Adult Intelligence Scale (ed 3). Palm Beach Gardens, FL, Pearson Psychological Corporation, 1997
27. Fine EM, Delis DC: California Verbal Learning Test, Children's Version. Palm Beach Gardens, FL, Pearson Psychological Corporation, 1994
28. Delis DC, Kramer JH, Kaplan E, et al: California Verbal Learning Test (ed 2). Palm Beach Gardens, FL, Pearson Psychological Corporation, 2000
29. Podell K: Purdue Pegboard, in Kreutzer JS, DeLuca J, Caplan B (eds): Encyclopedia of Clinical Neuropsychology. New York, NY, Springer, 2011
30. Woodcock R: Woodcock-Johnson, in Tests of Academic Achievement (ed 3). Rolling Meadows, IL, Riverside Publishing, 2001
31. Reynolds CR, Kamphaus RW: Behavior Assessment System for Children (BASC-3) (ed 3). Palm Beach Gardens, FL, Pearson Psychological Corporation, 2015
32. Greene JA, Trujillo S, Isquith PK, et al: Behavior Rating Inventory of Executive Function—Preschool Version. Lutz, FL, Psychological Assessment Resources, 2001
33. Gioia G, Isquith PK, Guy SC, et al: Behavior Rating Inventory of Executive Function. Lutz, FL, Psychological Assessment Resources, 2001
34. Harrison PL, Oakland T: Adaptive Behavior Assessment System (ed 2). Palm Beach Gardens, FL, Pearson Psychological Corporation, 2003
35. van der Plas E, Qiu W, Nieman BJ, et al: Sex-specific associations between chemotherapy, chronic conditions, and neurocognitive impairment in acute lymphoblastic leukemia survivors: A report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 113:588-596, 2021
36. Jednorog K, Altarelli I, Monzalvo K, et al: The influence of socioeconomic status on children's brain structure. PLoS one 7:e42486, 2012
37. Luby J, Belden A, Botteron K, et al: The effects of poverty on childhood brain development: The mediating effect of caregiving and stressful life events. JAMA Pediatr 167:1135-1142, 2013
38. Edelmann MN, Ogg RJ, Scoggins MA, et al: Dexamethasone exposure and memory function in adult survivors of childhood acute lymphoblastic leukemia: A report from the SJLIFE cohort. Pediatr Blood Cancer 60:1778-1784, 2013
39. Yakolev PI, Lecours AR: Regional development of brain early in life, in Minkowski A (ed): The Myelogenetic Cycles of Regional Maturation of the Brain. Oxford, United Kingdom, Blackwell, 1967. pp 3-170
40. Fry AF, Hale S: Relationships among processing speed, working memory, and fluid intelligence in children. Biol Psychol 54:1-34, 2000
41. Guo J, Han Y, Li Y, Reddick WE: Reduced brain microstructural asymmetry in patients with childhood leukemia treated with chemotherapy compared with healthy controls. PLoS One 14:e0216554, 2019
42. Kesler SR, Ogg R, Reddick WE, et al: Brain network connectivity and executive function in long-term survivors of childhood acute lymphoblastic leukemia. Brain Connect 8:333-342, 2018
43. Annett RD, Patel SK, Phipps S: Monitoring and assessment of neuropsychological outcomes as a standard of care in pediatric oncology. Pediatr Blood Cancer 62:S460-S513, 2015 (suppl 5)
44. Jacola LM, Partanen M, Lemiere J, et al: Assessment and monitoring of neurocognitive function in pediatric cancer. J Clin Oncol 39:1696-1704, 2021

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The Impact of Intensified CNS-Directed Therapy on Neurocognitive Outcomes in Survivors of Childhood Acute Lymphoblastic Leukemia Treated Without Cranial Irradiation

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Kevin R. Krull
Patents, Royalties, Other Intellectual Property: Royalties from Wolters Kluwer

Ching-Hon Pui
Leadership: Adaptive Biotechnologies
Honoraria: Novartis
Consulting or Advisory Role: Adaptive Biotechnologies
Research Funding: National Cancer Institute

No other potential conflicts of interest were reported.

APPENDIX

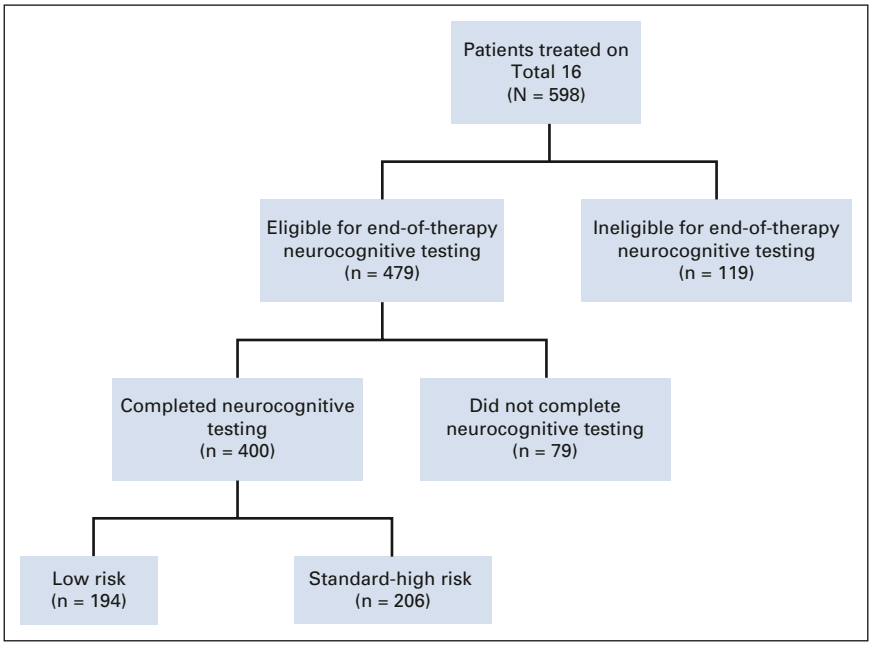

FIG A1. Study population and flowchart. Reasons for ineligibility for neurocognitive monitoring on Total 16 were as follows: Down syndrome (n = 12), English not primary language (n = 25), removed from treatment before the end of therapy (n = 54), and not offered consent (n = 28).

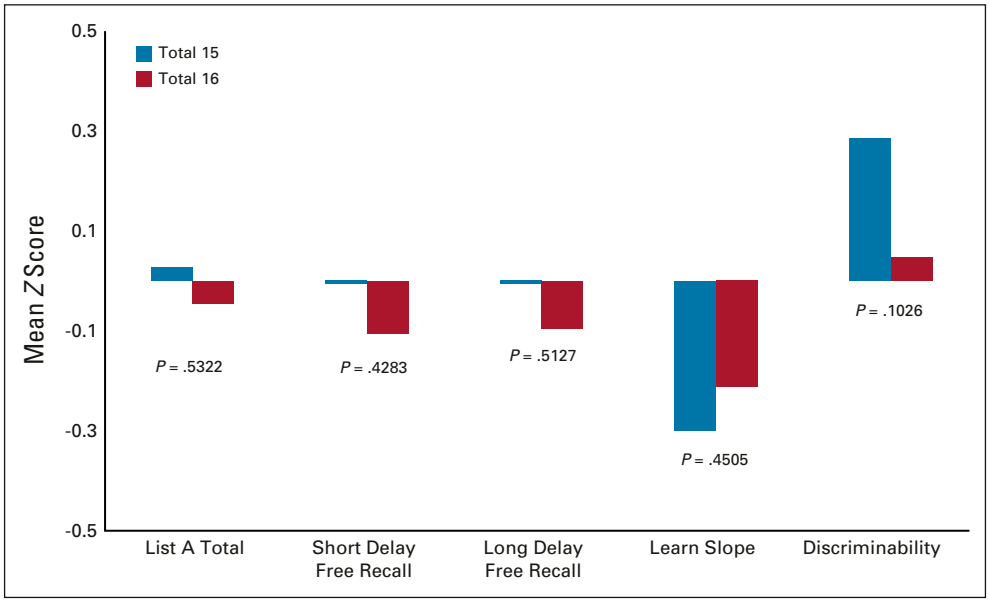

FIG A2. Learning and memory outcomes in patients at highest risk for CNS relapse from Total 15 or 16. Total 15, n = 112. Total 16, n = 200. Two-sided *P* values from one-way ANOVA comparing outcomes between Total 15 and Total 16. ANOVA, analysis of variance.

TABLE A1. Frequency of ITT by Treatment Risk Arm

ITT Frequency	Low-Risk, No. (%)	Standard-to-High Risk, No. (%)
9		1 (0.5)
10	1 (0.5)	
11	1 (0.5)	
12	2 (1.0)	
13	115 (59.3)	3 (1.5)
14		2 (1.0)
15		5 (2.4)
16		45 (21.8)
17	1 (0.5)	2 (1.0)
18	2 (1.0)	2 (1.0)
19		
20	2 (1.0)	2 (1.0)
21	**70 (36.1)**	1 (0.5)
22		3 (1.5)
23		8 (3.9)
24		13 (6.3)
25		11 (5.3)
26		27 (13.1)
27		**80 (38.8)**
28		**1 (0.5)**
	Total = 194 (100.0)	Total = 206 (100.0)

NOTE. Bold values indicate intensified ITT group. Cut points were based on the intensified ITT schedule; ITT was intensified during induction and continuation therapy for patients with T-cell ALL, higher-risk genomic features of ALL, or any number of leukemic blasts identifiable in the CSF at diagnosis. In the low-risk group, these patients were scheduled to receive 21 total ITT doses. In the standard/high risk group, these patients were scheduled to receive 27 doses. Planned ITT frequency was modified in some patients on the basis of protocol guidelines. Patients received less than originally planned on the basis of unanticipated toxicities and coming off protocol therapy, and more because of reemergence of CNS blasts with persistently negative minimal residual disease in marrow.

Abbreviations: ALL, acute lymphoblastic leukemia; ITT, triple intrathecal therapy.

TABLE A2. Neurocognitive Assessment Battery

Domain	Measure	Lower Age, years
Global intelligence	SB-5 Estimated IQ	3
Attention	Kiddie CPT or CPT-2	4
	BASC-2 Parent Rating	2
Working memory	WJ-3 Cog - Auditory Working Memory	4
	WISC-4 or WAIS-3 Digit Span Forward and Backward	6
Processing speed	WJ-3 Cog - Visual Matching, Decision Speed	3
Executive function	WJ-3 Cog - Retrieval Fluency	3
	BRIEF-P or BRIEF Parent Rating	2
Learning and memory	CVLT-C or CVLT-2	5
Fine motor speed	Purdue Pegboard	3
Academics	WJ-3 Ach—Letter-Word Identification, Spelling, Applied Problems	6
Adaptive skills	ABAS-2 Parent Rating	All ages

Abbreviations: ABAS-2, Adaptive Behavior Assessment System, Second Edition; BASC-2, Behavior Assessment Scales for Children, Second Edition; BRIEF, Behavior Rating Inventory of Executive Function; BRIEF-P, Behavior Rating Inventory of Executive Function, Preschool; CPT, Connors' Continuous Performance Test; CVLT, California Verbal Learning Test; IQ, intelligence quotient; SB-5, Stanford Binet Intelligence Scales, Fifth Edition; WAIS-3, Wechsler Adult Intelligence Scales, Third Edition; WISC-4, Wechsler Intelligence Scales for Children, Fourth Edition; WJ-3 Ach, Woodcock Johnson Test of Academic Achievement, Third Edition; WJ-3 Cog, Woodcock Johnson Test of Cognitive Abilities, Third Edition.

TABLE A3. Demographic and Clinical Characteristics for Eligible and Ineligible Patients

Demographic and Clinical Characteristics	Eligible (N = 479)	Ineligible (N = 119)	$P_{2\text{-sided}}$
Sex, No. (%)			
Female	201 (42.0)	47 (39.5)	.6250
Male	278 (58.0)	72 (60.5)	
Race, No. (%)			
White	377 (79.5)	87 (75.0)	.1598
Black	71 (15.0)	17 (14.7)	
Multiracial	15 (3.2)	12 (10.3)	
Asian	10 (2.1)	0 (0.0)	
American Indian, Alaskan Native	1 (0.2)	12 (10.3)	
Ethnicity, No. (%)			
Hispanic	32 (7.2)	33 (38.4)	< .0001
Non-Hispanic	444 (92.8)	86 (61.6)	
Insurance type, No. (%)			
Private	236 (49.3)	42 (35.3)	.0062
Public or none	243 (50.7)	77 (64.7)	

	Mean	SD	Mean	SD	$P_{2\text{-sided}}$
Age at diagnosis, years	7.19	4.70	7.66	5.40	.3459
ITT frequency	19.18	5.94	16.28	6.77	< .0001

NOTE. *P* value is from frequency or mean comparisons (chi-square or *t* test) between eligible and ineligible groups. For the purpose of frequency comparisons, race was collapsed into three levels (White, Black, and other).

Abbreviations: ITT, triple intrathecal therapy; SD, standard deviation.

TABLE A4. Neurocognitive Outcomes at the End of Therapy by Treatment Risk Arm

	Low-Risk		Standard-to-High Risk		
Neurocognitive Outcomes	**Mean**	**SD**	**Mean**	**SD**	***P*[b]**
Global intelligence					
Estimated IQ	–0.27	1.04	–0.14	0.89	.2056
Attention					
Omissions	0.40	1.29	0.69	2.69	.3380
Hit Reaction Time	–0.23	1.11	–0.14	1.19	.5500
Variability	0.62	0.97	0.47	1.19	.3380
Detectability	0.45	0.83	0.12	1.10	**.0114**
Beta	–0.03	0.76	0.13	1.11	.3380
Attention Problems[a]	0.12	1.00	0.14	1.01	.8743
Working memory					
Auditory Working Memory	0.35	0.90	0.08	0.79	**.0070**
Digit Span	–0.58	0.86	–0.41	0.98	.1267
Processing speed					
Visual Matching	–0.16	1.01	–0.50	1.09	**.0040**
Decision Speed	0.02	1.10	0.05	1.14	.8331
Executive function					
Retrieval Fluency	–0.29	0.88	–0.24	0.91	.6175
Global Executive[a]	0.24	1.13	0.32	1.19	.6175
Learning and memory					
List A Total	–0.15	0.99	0.09	0.97	.0670
Short Delay Free Recall	–0.15	0.97	–0.01	1.05	.3503
Long Delay Free Recall	–0.22	1.11	0.05	1.05	.0670
Learn Slope	–0.16	1.02	–0.15	0.99	.8939
Discriminability	0.12	1.27	0.10	1.22	.8939
Fine motor					
Purdue Pegs	–0.54	1.10	–0.70	1.24	.1804
Academics					
Letter Word Identification	0.03	0.99	–0.18	0.97	.0606
Spelling	0.00	0.97	–0.08	0.97	.4111
Applied Problems	–0.02	0.86	–0.24	0.83	**.0465**
Adaptive skills					
Global Adaptive[a]	–0.26	1.06	–0.32	1.15	.6158

NOTE. Low-Risk (N = 194). Standard-to-High Risk (N = 206). *Z*-score normative mean = 0, SD = 1. Bold values indicate results significant at $P < .05$, false discovery rate corrected for multiple comparisons by neurocognitive domain.

Abbreviations: IQ, intelligence quotient; SD, standard deviation.

[a]Caregiver ratings.

[b]Two-sided *P* value from one-way analysis of variance by treatment risk arm.

TABLE A5. Case-Control Analysis Comparing Neurocognitive Outcomes by Seizure Status

	Seizure Group (n = 11)		Control Group (n = 43)		
Neurocognitive Outcomes	**Mean**	**SD**	**Mean**	**SD**	***P*[b]**
Global intelligence					
Estimated IQ	–0.04	0.91	–0.23	1.06	.5763
Attention					
Omissions	0.86	1.08	0.26	0.99	.1067
Attention Problems[a]	–0.03	1.06	–0.02	1.08	.9882
Working memory					
Digit Span	–0.19	0.92	–0.58	0.84	.2872
Processing speed					
Visual Matching	–0.85	1.24	–0.34	1.12	.2093
Executive function					
Retrieval Fluency	–0.78	1.19	–0.23	0.78	.0837
Global Executive[a]	–0.47	0.78	0.29	1.27	.0796
Learning and memory					
Learn Slope	–0.06	1.02	–0.30	0.94	.5288
Fine motor					
Purdue Pegs	–0.98	1.05	–0.63	1.12	.3737
Academics					
Applied Problems	–0.79	0.76	–0.04	0.80	**.0095**
Adaptive skills					
Global Adaptive[a]	–0.70	1.29	–0.15	1.18	.2069

NOTE. *Z* score normative mean = 0, SD = 1. Seizure group = patients who experienced seizures after reinduction 1. Control group is matched on age at diagnosis, total frequency of ITT, and distribution of risk arm and patient sex. Bold values indicate results significant at $P < .05$.

Abbreviations: IQ, intelligence quotient; ITT, triple intrathecal therapy; SD, standard deviation.

[a]Caregiver ratings.

[b]Two-sided *P* value from one-way analysis of variance by seizure group.

TABLE A6. Case-Control Analysis Comparing Neurocognitive Outcomes by Infection Status

	Infection Group (n = 19)		Control Group (n = 76)		
Neurocognitive Outcomes	**Mean**	**SD**	**Mean**	**SD**	***P*[b]**
Global intelligence					
Estimated IQ	–0.37	0.83	–0.21	0.86	.4631
Attention					
Omissions	0.29	0.95	0.80	3.08	.5058
Attention Problems[a]	0.66	1.32	0.19	0.92	.1160
Working memory					
Digit Span	–0.27	1.00	–0.43	0.86	.5357
Processing speed					
Visual Matching	–0.42	0.77	–0.42	1.28	.9855
Executive function					
Retrieval Fluency	–0.56	0.71	–0.20	0.81	.0743
Global Executive[a]	0.57	1.41	0.25	0.99	.3099
Learning and memory					
Learn Slope	–0.12	0.57	–0.07	1.06	.8729
Fine motor					
Purdue Pegs	–1.00	1.56	–0.76	1.24	.4580
Academics					
Applied Problems	0.13	0.91	–0.26	0.86	.1059
Adaptive skills					
Global Adaptive[a]	–0.63	1.40	–0.30	1.09	.3294

NOTE. Infection group = patients with grade 4 or 5 infection during therapy. Control group is matched on age at diagnosis, total frequency of ITT, and distribution of risk arm and patient sex. SD = standard deviation. *Z* score normative mean = 0, SD, 1. Bold values indicate results significant at $P < .05$.

Abbreviations: IQ, intelligence quotient; ITT, triple intrathecal therapy.

[a]Caregiver ratings.

[b]Two-sided *P* value from one-way analysis of variance by infection group.