

# Excellent Therapeutic Efficacy and Minimal Late Neurotoxicity in Children Treated with 18 Grays of Cranial Radiation Therapy for High-Risk Acute Lymphoblastic Leukemia

## *A 7-Year Follow-Up Study of the Dana-Farber Cancer Institute Consortium Protocol 87-01*

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**BACKGROUND.** In the current study, the authors evaluated late neuropsychologic effects 7 years after diagnosis and the long-term survival in a cohort of patients treated for high-risk childhood acute lymphoblastic leukemia (ALL) with cranial radiation therapy. Efficacy and toxicity were evaluated in relation to patient age at diagnosis (age < or ≥ 36 months).

**METHODS.** Two hundred and one patients treated for high-risk ALL on the Dana-Farber Cancer Institute Consortium Protocol 87-01 were included, 147 of whom were in continuous complete disease remission and were eligible for cognitive testing. Sixty-one patients consented to undergo testing. All patients received 18 grays (Gy) of cranial radiation as a component of central nervous system treatment.

**RESULTS.** For all 201 patients, the 5-year overall survival (% ± the standard error) was 82% ± 2 and the 5-year event-free survival (% ± the standard error) was 75% ± 3. Only two patients developed a central nervous system recurrence. Intelligence quotient (IQ) and memory were at the expected mean for age, but performance on a complex figure drawing task was found to be reduced. Children who were age < 36 months at the time of diagnosis were found to have an IQ in the average range, but showed verbal deficits.

**CONCLUSIONS.** The results of the current study demonstrate excellent efficacy of therapy and relatively limited late neurotoxicity on a childhood ALL therapy protocol in which all evaluated patients had received 18 Gy of cranial radiation. Efficacious therapy that includes cranial radiation does not appear to necessarily incur a heightened risk for significant cognitive impairment. *Cancer* 2001;92:15-22. © 2001 American Cancer Society.

**KEYWORDS:** acute lymphoblastic leukemia, cranial irradiation, neuropsychologic toxicity, central nervous system, recurrence.

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**F**or children with acute lymphoblastic leukemia (ALL), cranial radiation therapy (CRT) has been proven to be highly effective in preventing disease recurrence in the central nervous system (CNS) and in enhancing event-free survival (EFS).<sup>1</sup> However, because of persistent concerns regarding the late effects of such therapy on cognition, the role of CRT in childhood ALL therapy remains controversial. Neuropsychologic studies document clinically significant cognitive deficits in children whose therapy included 24 grays (Gy) of CRT.<sup>2-5</sup> In response to the concerns raised, investigators decreased the CRT dose to 18 Gy or, for patients with a lower risk of disease recurrence, eliminated the CRT altogether in favor of a more intensive intrathecal drug with or without more intensive systemic chemotherapy. These strategies appear to diminish the severity of late cognitive sequelae of therapy.<sup>6,7</sup> More recently, reports of adverse late cognitive effects after CNS therapy without CRT have emerged.<sup>8-10</sup>

Implicit in the studies of neuropsychologic late effects is the overriding goal of providing information that will inform decisions concerning the optimal balance between efficacy and toxicity. However, to our knowledge nearly all published studies of late cognitive sequelae to date report the late effects of a therapeutic strategy without reference to the efficacy of that therapy. The therapy protocols on which the children were treated are occasionally, but not always, cited or described, and reports of therapeutic efficacy for the children who are the subjects of the studies are not always cited. Moreover, patient populations may be selected on a different basis for toxicity and efficacy studies derived from the same treatment protocols. In theory, toxicity could be substantially less with one treatment protocol compared with another, but at the considerable price of reduced efficacy. Or, a more toxic therapy might be applied when in fact a less toxic one is equally efficacious.

In the current study, we present data regarding both late neuropsychologic effects at 7 years after diagnosis and the long-term survival for a cohort of patients treated for high-risk ALL on the Dana-Farber Cancer Institute ALL Consortium Protocol 87-01, whose therapy included 18 Gy of CRT. Because children treated at young ages (age < 36 months) are believed to be at greater risk for adverse cognitive sequelae,<sup>11</sup> we evaluated efficacy and toxicity in relation to patient age at diagnosis.

## MATERIALS AND METHODS

Two hundred and one children treated for high-risk ALL on the Dana-Farber Consortium Protocol 87-01 at the Dana-Farber Cancer Institute, Boston, Massachu-

setts; Hopital St. Justine, Montreal, Quebec, Canada; San Juan Children's Hospital, San Juan, Puerto Rico; Maine Children's Cancer Program, Portland, Maine; University of Massachusetts Medical Center, Worcester, Massachusetts; University of Rochester Medical Center, Rochester, New York; and McMaster University Medical Center, Hamilton, Ontario, Canada, comprised the study sample. Another 26 children enrolled on Protocol 87-01 were not included in this follow-up study (11 were from 2 centers that did not participate in the neuropsychologic follow-up testing and 15 of the children had neurodevelopmental disabilities that predated the diagnosis of leukemia).

Neuropsychologic evaluations were performed between June 1996 and March 1999. Survival statistics were calculated as of March 2000. The investigation was performed after approval by the institutional review boards of all the participating institutions.

Newly diagnosed patients with ALL were enrolled on the Dana-Farber Consortium Protocol 87-01 between November 1987 and July 1991. At the time of diagnosis, the children were assigned to undergo one of two intensification treatment programs according to the risk of disease recurrence. Patients were considered at high risk (HR) if they met  $\geq 1$  of the following criteria: age < 2 years or > 9 years, a presenting leukocyte count  $\geq 20,000/\mu\text{L}$ , T-cell phenotype markers, radiologic evidence of a mediastinal mass, evidence of biphenotypic leukemia (coexpression of lymphoid and myeloid cell surface antigens), evidence of the Philadelphia chromosome, and/or clinical signs or cytologic evidence (presence of any blast cell in a cytocentrifuged cerebrospinal fluid specimen, regardless of cell count) of CNS leukemia. All other patients were considered to be in the standard risk (SR) group. Details of therapy on Protocol 87-01 have been published previously<sup>12</sup> and the protocol for HR patients is outlined in Table 1.

At the time of neuropsychologic follow-up, 46 children had died and 9 others were alive after disease recurrence ( $N = 8$ ) or induction failure ( $N = 1$ ). Of the remaining 146 children who were in continuous complete remission and therefore were eligible for testing, 85 did not undergo neuropsychologic testing for the following reasons: 60 did not respond or refused to participate, 18 lived too far away, and 7 did not undergo neuropsychologic testing for other reasons. Thus, the neuropsychologic follow-up study at a median of 7 years from the time of the initial diagnosis was based on 61 patients (42% of those patients eligible), whose characteristics are shown in Table 2. These characteristics were comparable to those of the 85 patients who were not tested.

**TABLE 1**  
Therapy for High-Risk Patients on the Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia Consortium Protocol 87-01<sup>a</sup>

Induction	Asparaginase × 1 dose on Day 0 (randomized): <i>E. coli</i> or Erwinia 25,000 IU/m <sup>2</sup> , or PEG, 2500 IU/m <sup>2</sup> Vincristine, 1.5 mg/m <sup>2</sup> (maximum = 2 mg on Days 5, 12, and 19) Prednisone, 40 mg/m <sup>2</sup> /day Days 5–26, doxorubicin, 30 mg/m <sup>2</sup> /dose on Days 5 and 6, methotrexate on Day 7 (randomized, 40 mg/m <sup>2</sup> or 4 gm/m <sup>2</sup> with leucovorin) IT cytarabine (dosed by age) on Days 5 and 19 <sup>b</sup>
CNS treatment	Cranial XRT, 1800 cGy <sup>c</sup> IT methotrexate/cytarabine (dosed by age) <sup>d</sup> twice weekly for 2 weeks concurrent with XRT, then every 18 weeks × 24 months
Intensification	Cycles every 3 weeks comprised of: vincristine, 2.0 mg/m <sup>2</sup> IV on Day 1 (maximum = 2 mg) 6-mercaptopurine, 50 mg/m <sup>2</sup> /day orally on Days 1–14 Prednisone, 120 mg/m <sup>2</sup> /day orally on Days 1–5 Doxorubicin, 30 mg/m <sup>2</sup> on Day 1 (until cumulative dose of 360 mg/m <sup>2</sup> is reached) Asparaginase, 25,000 IU/m <sup>2</sup> IM every week × 20 doses
Continuation (until 24 months CCR)	Cycles every 3 weeks as in intensification, except methotrexate, 30 mg/m <sup>2</sup> IV or IM every week; no asparaginase; no doxorubicin

*E. coli*: Escherichia coli; PEG: polyethylene glycosylated Escherichia coli L-asparaginase; IT: intrathecal; XRT: radiation therapy; CNS: central nervous system; cGy: centigrays; IV: intravenously; IM: intramuscular; CCR: complete continuous remission.

<sup>a</sup> Chemotherapy was dosed per kilogram for patients with a body surface area of ≤ 0.6 m<sup>2</sup>.

<sup>b</sup> Intrathecal cytarabine dosage: age < 1 yr: 15 mg; age ≥ 1 but < 2 yrs: 20 mg; age ≥ 2 but < 3 yrs: 30 mg; and age ≥ 3 years: 40 mg. Patients with central nervous system leukemia at diagnoses received twice weekly doses of intrathecal cytarabine until the cerebrospinal fluid was clear of blast cells on three consecutive examinations.

<sup>c</sup> Cranial radiation therapy randomization: 180 centigrays every day for 10 days or 90 centigrays twice daily for 10 days (randomized).

<sup>d</sup> Intrathecal methotrexate dosage: age < 1 yr: 6 mg; age ≥ 1 but < 2 yrs: 8 mg; age ≥ 2 but < 3 yrs: 10 mg; and age ≥ 3 years: 12 mg.

**TABLE 2**  
Characteristics of Patients Who Underwent Neuropsychologic Testing (N = 61)

Patient characteristics (N = 61)	
Age at diagnosis (yrs) (median, range)	4.6 (0.3–17.4)
Age < 36 months at diagnosis (%)	27.9
Age at evaluation (yrs) (median, range)	12.4 (8.0–25.5)
Male (%)	50.8
Randomized to receive high-dose methotrexate (%)	44.8
Randomized to receive hyperfractionated CRT (%)	36.1
Native language (%)	
English	63.9
Spanish	19.7
French	16.4
Parental education (%)	
Less than high school	15.0
High school graduate	27.0
Some college	23.0
College graduate	23.0
Postgraduate education	12.0

CRT: cranial radiation therapy.

## Methods

The neuropsychologic test battery included five representative subtests of the Wechsler Intelligence Scale for Children-III (WISC-III) or the Wechsler Adult Intelligence Scale, Revised (WAIS-R): Information, Vocabulary, Digit Span, Picture Arrangement, and Block Design.<sup>13</sup> Two of these subtests, the Vocabulary and Block Design,

permit the estimation of Full Scale intelligence quotient (IQ); the correlation of this dyad with Full Scale IQ is 0.9.<sup>14</sup> For children who did not speak English, the most recent edition of the Wechsler Scale in their native language was used. The Rey-Osterrieth Complex Figure (ROCF) Test, Copy and Immediate Memory conditions also was administered.<sup>15</sup> This nonverbal instrument is sensitive to executive function, memory, visuospatial reasoning, and motor output and reliably distinguishes children with learning disabilities.<sup>16</sup> Declarative memory was assessed using the Visual and Verbal Learning subtests from the Wide Range Assessment of Memory and Learning (WRAML).<sup>17</sup> Because the norms for this test only reach 17 years, the 17-year norms were used for the few individual patients who were older. For children who did not speak English, the Verbal Learning subtest was translated into their native language. We used a relatively brief battery to enhance the reliability and comparability of data across the various institutions and to encourage compliance. This approach also facilitated testing for a study group in which a substantial portion of the children did not speak English. Academic achievement was not assessed because of the lack of comparability of measures across language and cultural groups.

## Statistical Methods

Overall survival (OS) was the time from the initial diagnosis to death from any cause and EFS was the time from the initial diagnosis to induction death,

**TABLE 3**  
**Five-Year Overall Survival and Event-Free Survival for 201 High-Risk Patients Treated on the Dana-Farber Consortium Protocol 87-01 (1987-1991)**

Patient group	No. of patients	No. of deaths	5-year OS (%) (95% CI)	No. of events	5-year EFS (%) (95% CI)	No. of CNS events
All patients	201	47	82 (77, 88)	56	75 (69, 81)	2
Gender						
Male	123	32	79 (71, 86)	37	72 (64, 80)	1
Female	78	15	88 (81, 95)	19	79 (70, 88)	1
Age at diagnosis (mos)						
< 36	49	14	76 (63, 88)	14	73 (61, 86)	2
≥ 36	152	33	85 (79, 90)	42	75 (68, 82)	1

OS: overall survival; 95% CI: 95% confidence interval; EFS: event-free survival; CNS: central nervous system.

A total of 227 high-risk patients were treated on Protocol 87-01. Twenty-six were excluded from the current study for the following reasons: the child was treated at an institution that did not participate in the neuropsychologic follow-up ( $N = 11$ ) or the child had a neurodevelopmental condition predating the leukemia diagnosis ( $N = 15$ ).

induction failure, remission death, or disease recurrence, whichever occurred first. OS and EFS were estimated using the Kaplan–Meier method<sup>18</sup> and standard errors for the 5-year estimates were calculated using the Greenwood formula.<sup>19</sup>

Descriptive statistics for the neuropsychologic tests were generated to characterize the sample. Means, medians, and standard deviations (SD) then could be compared with expected population statistics. Estimated IQ scores  $\leq 90$  and subtest scaled scores (WISC-III and WRAML)  $\leq 8$  ( $2/3$  SD) were considered to be “low performance.” In a normal population, 25% of individuals would be expected to obtain scores  $< 2/3$  SD. For the ROCF, organization scores for copy and recall at or below the 25th percentile for age were considered “low performance.” These levels were set to be clinically meaningful. Ninety-five percent confidence intervals (95% CI) (not adjusted for multiple comparisons) were calculated based on the binomial distribution using the Wilson formula.<sup>20</sup> Logistic regression was used for group comparisons.

## RESULTS

### Overall Survival and Event-Free Survival

Efficacy data are presented in Table 3, stratified by age at diagnosis and gender. The median follow-up was 9.1 years, based on a reverse censoring method.<sup>21</sup> For all 201 patients, the 5-year OS%  $\pm$  the standard error was 82%  $\pm$  2 and the 5-year EFS% was 75%  $\pm$  3. Only 2 of the 201 patients (1.0%) had a CNS event. Differences in outcome according to gender and patient age at diagnosis were not statistically significant.

### Neuropsychologic Outcome

Table 4 displays the means, medians, SDs, and percent “low performance” for the IQ tests, the ROCF

subtests, and the WRAML subtests. The mean values were at the expected means based on population norms. Fifteen of the 61 children (25%) had estimated IQ scores  $\leq 90$ , a finding that is consistent with expectations for the normal population. Of the five subtests, an elevation in poor performance was observed for Digit Span and Picture Arrangement, for which the 95% CI was  $> 25\%$ . WRAML scores were consistent with those expected for both Verbal and Visual Learning, but the ROCF scores showed an elevated prevalence of low performance.

Table 5 shows the neuropsychologic outcomes according to groups defined by age at diagnosis as well as gender and randomized induction methotrexate dose and CRT dose schedule. Probability estimates that exceed the expected 25% (by 95% CIs) reliably are shown in *italic* type. Estimated IQ and both WRAML subtests consistently were in the expected range, but nearly all the estimates for both conditions of the ROCF were elevated.

Similar estimates were calculated for the five subtests of the WISC-III. For those children diagnosed at age  $\geq 36$  months, none of the estimates was elevated. By contrast, for those children diagnosed at age  $< 36$  months, estimates of the probability of low performance ( $p^{\text{low}}$ ) were significantly elevated for both the Vocabulary ( $p^{\text{low}} = 0.53$ ; 95% CI, = 0.31, 0.74) and Digit Span ( $p^{\text{low}} = 0.71$ ; 95% CI, = 0.47, 0.87) subtests. Evaluation by gender revealed elevated estimates for Picture Arrangement for females ( $p^{\text{low}} = 0.50$ ; 95% CI, = 0.33, 0.67) and Digit Span for males ( $p^{\text{low}} = 0.48$ ; 95% CI, = 0.32, 0.65). Finally, there were elevated estimations for Digit Span ( $p^{\text{low}} = 0.50$ ; 95% CI, = 0.34, 0.67) and Picture Arrangement ( $p^{\text{low}} = 0.47$ ; 95% CI, = 0.31, 0.63) in children randomized to the standard

**TABLE 4**  
**Neuropsychologic Outcomes for Patients Treated on the Dana-Farber Consortium Protocol 87-01**

Neuropsychologic measure	Continuous measure	Percent "low performance" <sup>a</sup> (95% CI)
Wechsler Intelligence Scale for Children—III		
Estimated Full Scale IQ	Mean ± SD	
Information	100 ± 14	25% (16%, 37%)
Vocabulary	10 ± 3	22% (33%, 45%)
Digit Span	10 ± 2	28% (18%, 40%)
Picture Arrangement	9 ± 3	43% (31%, 55%)
Block Design	10 ± 3	38% (27%, 50%)
Wide Range Assessment of Memory and Learning	10 ± 4	33% (22%, 45%)
Verbal Learning	11 ± 3	16% (9%, 28%)
Visual Learning	11 ± 3	18% (10%, 29%)
Rey-Osterrieth Complex Figure (median)		
Copy	Median	
Recall	25	51% (39%, 63%)
	50	44% (33%, 57%)

95% CI: 95% confidence interval; SD: standard deviation; IQ: intelligence quotient.

Expected means for population are 100 for estimated intelligence quotient, 10 for Wechsler Intelligence Scale for Children—III subtests, and 50 for Rey-Osterrieth Complex Figure.

<sup>a</sup> "Low performance" ≤ 90 for estimated intelligence quotient, ≤ 8 for Wechsler Intelligence Scale for Children—III subtests, ≤ 25% for Rey-Osterrieth Complex Figure. *p*<sup>low</sup> indicates the probability of low performance. Items in italics are those in which the probability that the prevalence of low performance exceeds the expected prevalence.

dose of methotrexate, but not in those children randomized to the high dose.

The possibility that children who were younger at the time of diagnosis would be more vulnerable to late cognitive effects was of particular interest. Comparisons of children who were age ≤ 36 months at the time of diagnosis with the remainder of the sample were performed using logistic regression, after adjusting for the effects of parental education, native language, gender, and methotrexate dose. Children who were younger at the time of diagnosis were more likely to have low performance on the WISC-III Vocabulary (odds ratio [OR] = 34.1, 95% CI, = 3.7, 312.5; *P* < 0.01) and Digit Span (OR = 5.2, 95% CI, = 1.3, 21.4; *P* < 0.03) subtests. Differences for the other tests were not found to achieve statistical significance.

## DISCUSSION

Children treated for high-risk ALL on the Dana-Farber Cancer Institute Protocol 87-01, which included 18-Gy CRT as a component of CNS treatment, experienced an excellent 5-year OS rate of 82% and an exceptionally low rate (approximately 1% of all cases) of disease recurrence in the CNS. In addition, despite their hav-

ing received 18 Gy of CRT, the performance of these patients on basic measures of intelligence and memory 7 years after diagnosis generally was in the average range, similar to that of the general population. Only 36% of the children had parents who were college graduates (compared with 44% in the standardization sample for the WISC-III) and thus it is unlikely that the good performance of these children could be attributed to environmental enrichment. Nor is it likely that the performance of these children as a group was unduly low compared with what might have been expected given their social background.

However, there was a general elevation in the prevalence of low performance on the ROCF test, a neuropsychologic test that measures a child's ability to manage novel complex information and that can distinguish children with learning problems from normative controls. This finding suggests that these children can be particularly challenged as novelty and complexity increase, despite their normal IQ. In a prior study,<sup>22</sup> we demonstrated that the poor performance on this task of children who were ALL survivors, most notably their ability to recall the figure, was easily normalized by providing cues regarding strategy, implicating metacognitive processes (i.e., knowing about knowing) rather than more basic perceptual or motor function. This result has direct implications for educational intervention.

Children who were age < 36 months at the time of diagnosis appeared to be somewhat more vulnerable to CNS toxicity, a finding that is consistent with findings from other studies.<sup>11,23</sup> Children who were age < 36 months at the time of diagnosis performed somewhat more poorly on the WISC-III Vocabulary and Digit Span subtests. This result suggested that these children were more vulnerable to cognitive processing deficits even though their IQ scores were intact.

In prior studies,<sup>24,25</sup> we observed a synergistic interaction between high-dose methotrexate and CRT in females, a phenomenon that was not noted in the current study. This most likely reflects sampling differences, in which the target group comprised a small proportion of the total sample. It also is conceivable that the longer interval for follow-up (7 years) in the current study allowed time for compensation to occur.

The absence of significant adverse cognitive outcomes among children treated with CRT is noteworthy, given widespread assumptions regarding radiation-related neurotoxicity. Studies that have compared outcomes in children who were treated with or without CRT at the 18-Gy dose have yielded mixed results. Some authors have reported an increased risk for cognitive late effects associated with

**TABLE 5**  
Neuropsychologic Outcomes for Patients Treated on the Dana-Farber Consortium Protocol 87-01, According to Patient Characteristics

	No. of patients	Wechsler Intelligence Scale for Children—III Estimated Full Scale IQ		Rey-Osterrieth Complex Figure - Copy	
		Mean $\pm$ SD	p <sup>low</sup> <sup>a</sup> (95% CI)	Median	p <sup>low</sup> (95% CI)
Age < 36 mos	17	98 $\pm$ 17	35% (17%, 58%)	25	59% (36%, 78%)
Age $\geq$ 36 mos	44	101 $\pm$ 12	20% (11%, 34%)	50	48% (34%, 62%)
Males	31	101 $\pm$ 13	23% (11%, 40%)	50	48% (32%, 65%)
Females	30	100 $\pm$ 14	27% (14%, 44%)	25	53% (36%, 70%)
Standard-dose MTX	34	102 $\pm$ 14	20% (10%, 37%)	37.5	50% (34%, 66%)
High-dose MTX	27	98 $\pm$ 13	30% (16%, 48%)	25	52% (34%, 69%)
Standard XRT	39	101 $\pm$ 14	23% (13%, 38%)	50	49% (34%, 64%)
Investigational XRT	22	99 $\pm$ 13	27% (13%, 48%)	25	55% (35%, 73%)

  

	No. of patients	Wide Range Assessment of Memory and Learning			
		Verbal memory mean $\pm$ SD	p <sup>low</sup> (95% CI)	Visual memory mean $\pm$ SD	p <sup>low</sup> (95% CI)
Age < 36 mos	17	11 $\pm$ 3	17% (6%, 41%)	9 $\pm$ 3	35% (17%, 58%)
Age $\geq$ 36 mos	44	11 $\pm$ 3	16% (8%, 29%)	11 $\pm$ 3	11% (5%, 24%)
Males	31	11 $\pm$ 3	9% (3%, 25%)	11 $\pm$ 2	16% (7%, 33%)
Females	30	11 $\pm$ 3	23% (12%, 41%)	10 $\pm$ 3	20% (10%, 37%)
Standard-dose MTX	34	11 $\pm$ 3	20% (10%, 37%)	11 $\pm$ 3	23% (12%, 40%)
High-dose MTX	27	11 $\pm$ 3	11% (4%, 28%)	11 $\pm$ 3	11% (4%, 28%)
Standard XRT	39	11 $\pm$ 3	13% (6%, 27%)	10 $\pm$ 3	23% (13%, 38%)
Investigational XRT	22	11 $\pm$ 3	23% (10%, 43%)	11 $\pm$ 3	9% (3%, 28%)

IQ: intelligence quotient; SD: standard deviation; p<sup>low</sup>: probability of low performance; 95% CI: 95% confidence interval; MTX: methotrexate; XRT: radiation therapy.

Expected means for populations are 100 for Estimated intelligence quotient, 50<sup>th</sup> percentile for Rey-Osterrieth Complex Figure.

<sup>a</sup> Low performance =  $\leq$  90 for estimated intelligence quotient,  $\leq$  25<sup>th</sup> percentile for Rey-Osterrieth Complex Figure. Items in italics are those in which the probability that the prevalence of low performance exceeds the expected prevalence.

CRT<sup>11,26-28</sup> whereas others have not.<sup>7,10</sup> This variability could reflect methodologic issues in the studies or it could be a function of the therapeutic context within which CRT is given. In any event, the assumption that CRT inevitably increases the risk for significant neurotoxicity remains open to question.

However, the current study does have significant limitations. The neuropsychologic battery was brief and would not have been sensitive to the broader range of subtle deficits in information processing that could compromise function in children treated for ALL, and we were unable to measure academic achievement effectively. We were concerned that a more comprehensive battery might have been vulnerable to poor reliability, especially given the three different native languages of the children and the multiple treating institutions. Similarly, achievement tests were not comparable across the three different language groups and educational systems. In prior studies,<sup>5,23,24</sup> we were able to demonstrate clear group differences using a similar battery with fewer participants. In a similar cross-linguistic situation, Jankovic

et al.<sup>11</sup> reported data regarding the IQ test only. Moreover, from a clinical perspective, it is not clear that subtle deficits would outweigh treatment efficacy, even if they had been demonstrated.

Another concern is that neuropsychologic testing was completed for less than half the eligible participants. We believe that several factors contributed. First, by 7 years after diagnosis, 12% of the children had moved away from the area in which the institution at which they had been treated was located. Second, approximately 40% of eligible families declined to participate. Some families who refused commented that they believed they "did not need the testing," suggesting that the children were doing well functionally. We did compare participants with nonparticipants based on treatment and demographic variables and found no differences.

Although SR patients were treated without CRT on the current study protocol, there was an unanticipated high rate of disease recurrence among males,<sup>27</sup> the majority of whom received additional therapy that included CRT. Thus, we had insufficient power to

evaluate differences between patients treated with and those treated without CRT. Because we were unable to compare the HR patients with a group treated without CRT, we do not know to what extent the more specific deficits we did observe (e.g., complex figure drawing) were associated with CRT specifically or with the disease and its other therapy more generally. Furthermore, because the design was cross-sectional, we do not know to what extent the apparently normal cognitive performance of these children actually might reflect some decline over time. Finally, we were not able to address within the context of this protocol the question of whether an alternative therapeutic approach without CRT could achieve equal efficacy and similarly reduced toxicity.

In the current study, we demonstrated excellent therapeutic efficacy in tandem with cognitive outcomes that generally were in the expected range for the general population on a treatment protocol for HR ALL patients that included 18 Gy of CRT. However, more subtle cognitive sequelae, such as those reflected in diminished performance on complex figure drawing, could have functional consequences. Nonetheless, it is clear that efficacious therapy that includes CRT does not necessarily incur a heightened risk for significant cognitive impairment. Careful analysis and comparison of protocols may offer clues as to why CRT may be associated more frequently with adverse sequelae in some contexts compared with in others.

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