Neurocognitive Outcome in Very Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia After Treatment With Chemotherapy Only

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Background. There is a concern regarding long-term cognitive late effects after treatment for acute lymphoblastic leukemia (ALL). The present study assessed neuropsychological function in very long-term childhood ALL survivors treated with chemotherapy only. We also investigated associations between neurocognitive performance and individual treatment load. ***Procedure.*** One-hundred and twelve adult ALL survivors, diagnosed 1970–2002 before age 16 and treated with chemotherapy only, and 100 comparison peers underwent neuropsychological tests covering processing speed, executive functions, working memory, and verbal learning and memory. Individual cumulative doses of cytostatic agents were extracted from the medical records for each patient. ***Results.*** Mean age at diagnosis for survivors was 6.3 years and mean follow-up time was 22.6 years. There was no difference in general intellectual ability between survivors and comparison peers. However, survivors performed significantly more poorly in the neurocognitive domains' processing speed ($P = 0.003$, Cohen's d 0.48), executive functions, and working memory (both $P < 0.001$, Cohen's d 0.81–0.95). Among survivors, the rates of poor neurocognitive performance (>1.5 SD below control mean) for processing speed was 22%, executive functions 31%, working memory 34%, and verbal learning and memory 16%. Comparing survivors with poor versus normal neurocognitive performance, we found no difference with respect to cumulative doses of any of the cytostatic agents, age at diagnosis, or gender. ***Conclusions.*** Very long-term survivors of childhood ALL treated exclusively with chemotherapy showed no impairment in general intellectual ability, but significantly poorer performance in several neurocognitive domains than comparison peers. However, no associations emerged between neurocognitive impairment and treatment burden. Pediatr Blood Cancer

Key words: acute lymphoblastic leukemia; childhood cancer survivor; CNS-directed chemotherapy; cognitive function; late effects

INTRODUCTION

Acute lymphoblastic leukemia (ALL) accounts for approximately one-fourth of childhood cancers below the age of 16 in Norway.[1] Over the past few decades, 5-year-survival rates for childhood ALL in the Nordic countries have improved substantially and are approaching 90%.[2] This improvement has led to increased focus on late effects in long-term (≥5 years after diagnosis) survivors of ALL,[3] with neurocognitive late effects as one of the major concerns.

Central nervous system (CNS)-directed therapy is an essential part of ALL treatment. Prophylactic CNS-directed radiotherapy has been largely abandoned due to its detrimental effects on brain development and intellectual functioning.[4] In more current treatment protocols, intensified CNS-directed chemotherapy, with intravenous (IV) and intrathecal (IT) methotrexate (MTX) as major backbones, has replaced radiotherapy.

However, chemotherapy-based CNS-directed treatment may have a negative impact on cognitive functioning in ALL survivors as well, although likely to a lesser extent than radiotherapy.[5,6] General intellectual ability has been the main focus in early studies on cognitive outcome and does not seem to be affected markedly by ALL-treatment based on chemotherapy only.[7–9] Recent research has concentrated on more specific cognitive abilities and ALL survivors have been reported to show deficits in several neurocognitive domains, such as processing speed, attention, executive functions, and working memory.[5,6,10,11]

As brain development continues into early adulthood,[12] long-term cognitive outcome in ALL survivors may not become evident until years after completion of treatment. Until now, follow-up time in ALL survivors treated exclusively with chemotherapy has been limited, and thus, little is known about long-term neurocognitive functioning in ALL survivors who have lived for more than 10 years after their diagnosis.

In Norway, ALL treatment has been mainly based on CNS-intensified chemotherapy since 1975—in most cases without radiotherapy. This gave us the possibility to investigate very long-term neurocognitive outcome after CNS-directed chemotherapy in a larger group of ALL survivors not treated with radiotherapy, with a follow-up time of up to 40 years. The aim of our study was to assess both general intellectual ability and specific neurocognitive functions, with focus on processing speed, executive functioning, working memory, and verbal learning and memory. In addition, we aimed to explore associations between

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neurocognitive performance and individual treatment burden and other disease-related factors.

METHODS

Participants

This study, which is part of a larger cross-sectional survey of late effects after childhood ALL, included 112 long-term survivors. The Cancer Registry of Norway identified all individuals diagnosed with ALL from 1970 to 2002 at age below 16 years in the South-Eastern Region of Norway (covering approximately half of the Norwegian population). Adults (≥18 years) treated at Oslo University Hospital and alive in 2009 were eligible. Of the 210 survivors that fulfilled those criteria, 160 survivors agreed to participate, and 140 completed the clinical examination. Twenty survivors who had received cranial radiotherapy were excluded. Of the remaining 120 survivors, 112 completed the neuropsychological test battery (Supplemental Fig. S1).

A comparison group was obtained from an ongoing research project at the Department of Psychology, University of Oslo.[13] Participants were recruited through newspaper advertisements, and among local students and employees. Standardized health screening interviews were conducted and participants were required to be fluent Norwegian speakers, have normal or corrected to normal vision and hearing, and no self-reported neurological or psychiatric diseases. From this sample, we drew 100 comparison peers that had completed an identical neuropsychological test battery matched as closely as possible for age and gender to the survivors on a group level.

The Regional Committee for Medical and Health Research Ethics approved the study. All participants gave written informed consent.

Neuropsychological Assessment

General intellectual ability (IQ) was estimated using the two-subtest form of the Wechsler abbreviated scale of intelligence (WASI; Vocabulary and Matrices Reasoning).[14] ***Processing speed*** was assessed by the time to complete the Color Naming and Word Reading conditions of the *Color–word interference test (CWIT)* from the Delis–Kaplan System (D-KEFS).[15] ***Executive functions*** were assessed by completion time of the inhibition and the inhibition/shifting conditions of the *CWIT* (*D-KEFS*). Additionally, to extract the *interference effect*, a measure of the executive function inhibition controlled for processing speed, the ratio between the times to complete the inhibition condition (CWIT 3), and the color naming condition (CWIT 1) of the *CWIT Test* was calculated. A combined *interference effect* and s*hift cost* variable, a measure of the interference and flexibility aspects of executive functioning, was calculated as the ratio between the times to complete the inhibition/shifting condition (CWIT 4) and the color naming condition (CWIT 1). ***Working memory*** was assessed by the letter memory and the keep track task. The *letter memory task* was adapted by Miyake et al.[16] from Morris and Jones[17] letters were presented serially for 2,000 msec/letter on a computer monitor. The task was to recall and write down the last four letters presented in the list. The number of letters presented randomly varied between 5, 7, 9, and 11 across trials to ensure that participants would continuously update their working memory representations until the end of each trial. After practicing on two trials, the participants performed 12 test trials for a total of 48 letters recalled. The dependent measure was the total number of letters recalled correctly. The *keep track task* was originally adapted by Miyake et al.[16] from Yntema[18] Participants were first shown several target categories on the lower half of the computer screen. Sixteen words, including 2 or 3 exemplars from each of six possible categories (animals, car brands, colors, countries, fruits, and relatives), were then presented serially and in random order for 2,000 msec apiece, with the target categories remaining at the bottom of the screen. The task was to remember the last word presented in each of the target categories and then write down these words at the end of the trial. Thus, participants had to continuously update their working memory representations for the target categories. Participants practiced on two trials with two and three target categories, respectively. The task itself consisted of three trials with three, three trials with four, and three trials with five target categories. The total number of words recalled correctly was the dependent measure. ***Verbal learning and memory*** included the total items recalled from the five learning trials and the 30 min delayed free recall scores of the second edition of the *California verbal learning test (CVLT-II)*.[19]

In addition to investigating the neuropsychological test raw scores, we standardized and averaged the raw scores of the tests within each domain to calculate a composite z-score (for principal components analysis, see Supplemental Table SI). A composite z-score of more than 1.5 SD below control mean was classified as poor performance in the respective domain as opposed to normal performance (≥ −1.5 SD).[20]

Disease and Treatment Characteristics in Survivors

Information on the course of disease and treatment was obtained from the patients' records. During the years from 1970 to 2002, ALL treatment underwent substantial changes as to type of chemotherapy regimens and the cumulative doses of the cytostatic drugs. Prevention of CNS leukemia always included IT methotrexate. Other common elements were a 5-to-6-week induction period with oral prednisolone and vincristine, and an oral maintenance therapy with methotrexate and 6-mercaptopurine, reinforced by repeated vincristine injections and short steroid courses with prednisolone or dexamethasone. In Norway, routine prophylactic CNS-directed radiotherapy was systematically replaced by the combination of IV and IT MTX as early as 1975, in some patients even earlier.[21,22] In 1981, the first common Nordic protocols were introduced by Nordic Society of Paediatric Haematology and Oncology (NOPHO) and included increasing doses of anthracyclines and intravenous intermediate-dose methotrexate (0.5–1 g/m^2), as well as stratification according to risk groups.[23] Following the introduction of the NOPHO ALL-92 protocol in 1992, all patients received high-dose methotrexate (5–8 g/m^2) courses, and high-dose cytarabine (2 g/m^2) was added for high-risk patients.[23] Details of the treatment protocols (Norwegian protocols until 1980, NOPHO protocols from 1981) have been described previously,[21–23] and survival rates have shown to be among the highest in Europe and comparable to the US.[24,25] As treatment was not uniform throughout the inclusion period and varied within the different protocols depending on risk stratification, we chose to assess treatment load for each survivor individually, calculating cumulative doses of all cytotoxic agents

and the number of intrathecal methotrexate injections from the treatment charts.

Statistics

The statistical analyses were performed with IBM SPSS statistics 20. Group comparisons between survivors and comparison peers included *t* tests for continuous data and χ^2 tests for categorical data. Nonparametric tests were used when appropriate. For the neuropsychological performance measures, we compared raw scores for each subtest and the four composite z-scores in survivors and comparison peers by means of linear regression, adjusting for age, gender, and years of education (based on highest level of completed education). Statistically significant group differences were examined for clinical significance with effect sizes (ESs) using Cohen's coefficient d. ES values of 0.2–0.5 were considered as small, 0.5–0.8 as moderate, and 0.8 and above as large.[26]

To explore associations between poor neuropsychological performance and disease- and treatment-related factors in survivors, bivariate logistic regression analyses were performed with various independent variables, using the dichotomized composite z-scores of the four cognitive domains as the dependent variable (poor vs. normal performance as reference). The strength of associations was expressed as odds ratios (ORs) and 95% confidence intervals (CI) are reported. Due to multiple testing, however, with partially correlated variables (which would have made a strict Bonferroni correction a too conservative approach), we set the significance level at $P < 0.01$. All tests were two sided.

RESULTS

Demographics and Clinical Characteristics

Table I provides a summary of demographic characteristics for survivors and comparison peers, as well as disease and treatment characteristics for survivors. There were no group differences between survivors and comparison peers concerning age or gender, but comparison peers had completed more years of education.

For ALL survivors, mean age at diagnosis was 6.3 years, and mean follow-up time was 22.6 years. Eight survivors had experienced a relapse and two had undergone allogeneic hematopoietic stem cell transplantation (without irradiation). Three survivors had been diagnosed with CNS-involvement. For two of the oldest survivors (diagnosed 1972/1973), exact cumulative doses of cytostatic agents were not available. For the remaining 110 survivors, complete treatment data were accessible (Table I). There were no differences concerning gender distribution, age at diagnosis, age at investigation or follow-up time between participating survivors, and eligible non-participants (Supplemental Table SII).

TABLE I. Demographic Characteristics for Childhood ALL Survivors and Comparison Peers

Variables	Survivors (N = 112)	Comparison peers (N = 100)	Group difference (*P*)
Demographics			
Female gender, N (%)	58 (52)	56 (56)	0.54
Age at investigation, mean (SD, range)	28.4 (7.2, 18–46)	29.7 (8.0, 20–48)	0.20
Years of education, mean (SD, range)	13.8 (2.5, 10–18)	14.9 (2.2, 10–18)	0.001
Cancer-related characteristics			
Age at diagnosis, mean (SD, range)	6.3 (4.0, 0–15)		
Age at diagnosis <5 years, N (%)	53 (47)		
Follow-up time, mean (SD, range)	22.6 (7.2, 7–40)		
Treatment period, N (%)			
1970–1981	26 (23)		
1982–1991	49 (44)		
1992–2002	37 (33)		

Cumulative doses of cytotoxic agents (N = 110)[a]	N (%)[b]	Median (range)[c]
Methotrexate, number of intrathecal injections[d]	109 (99)	13 (3–36)
Methotrexate IV (g/m^2)[e]	106 (96)	21.0 (1.0–64.0)
High-dose methotrexate	62 (56)	32 (15–64)
Intermediate-dose methotrexate	44 (40)	1.5 (1.0–8.0)
Steroids, total dose (g/m^2)[f]	110 (100)	4.4 (1.9–14.9)
Dexamethasone treatment	29 (26)	0.24 (0.24–0.84)
Vincristine	110 (100)	22 (8–102)
Cytarabine (g/m^2)[g]	58 (53)	21.0 (0.02–95.2)
High dose	33 (30)	24.0 (9.8–95.2)
Low-dose only	25 (23)	1.8 (0.02–3.8)
Anthracyclines (doxorubicin-equivalent)	86 (78)	120 (40–510)
Duration of oral maintenance treatment, months[h]	110 (100)	30.7 (3.9–75.7)

Cancer-related characteristics and cumulative doses of cytostatic agents in childhood ALL survivors.

[a]Exact cumulative doses of cytotoxic agents not available for two patients. Unit: mg/m^2 body surface if not stated otherwise; [b]Number (percentage) of patients that received the drug; [c]For patients that received the drug; [d]Age-adjusted doses. Two patients received triple IT (methotrexate, cytarabine, prednisone)—these injections were counted as methotrexate injections and not analysed separately; [e]IV, intravenous. High-dose methotrexate: 5 or 8 g/m^2/administration. Intermediate-dose methotrexate: 0.5 or 1 g/m^2/administration; [f]Expressed as prednisolone-equivalent: 1 mg dexamethasone equivalent to 6.5 mg prednisolone; [g]High-dose cytarabine: 2 g/m^2/administration. Low-dose cytarabine: 75 mg/m^2/administration; [h]Methotrexate (20 mg/m^2 weekly) and 6-Mercaptopurine (50–75 mg/m^2 daily), adjusted to target leucocyte count 1.5–3.5.

Neuropsychological Performance in Survivors Versus Comparison Peers

Mean estimated IQ was 113.9 in survivors and 112.0 in comparison peers, with no significant group difference (Table II). Survivors performed more poorly than comparison peers on almost all other neurocognitive tests. The differences were highly significant, with medium to large effect sizes for the CWIT color naming subtest in the domain processing speed (P 0.001, Cohen's d 0.52), and all subtests in the domains executive functions ($P < 0.001$, Cohen's d 0.65–0.76) and working memory ($P < 0.001$, Cohen's d 0.78–0.88). In contrast, we found no difference in processing speed between survivors and comparison peers for the CWIT word reading subtest. In the executive function domain, the calculated CWIT interference effect was significantly larger in survivors than in comparison peers (ES 0.50). No difference was seen in the combined interference/shift cost effect. Effect sizes in the domain of verbal learning and memory were small, and the group difference between survivors and comparison peers was only significant for the CVLT-II total recall across the five learning trials, not for the delayed recall measure. However, this difference did not meet the conservative P value threshold of 0.01 when controlling for processing speed ($P = 0.03$) and disappeared when controlling for working memory ($P = 0.90$).

Figure 1 shows the mean differences in composite scores between survivors and comparison peers for the four domains tested, adjusted for age, sex, and education. Survivors had poorer composite scores than comparison peers in three out of four domains. Effect sizes were small to medium for the domain processing speed (mean difference −0.50, 95%CI −0.82 to −0.18, $P = 0.003$, ES 0.48), and large for the domains executive functions (mean difference −0.91, 95%CI −1.23 to −0.58, $P < 0.001$, ES 0.81) and working memory (mean difference −1.02, 95%CI −1.32 to −0.73, $P < 0.001$, ES 0.95). For verbal learning and memory, there was a trend toward poorer performance in survivors, though not significant (mean difference −0.31, 95%CI −0.57 to −0.05, $P = 0.02$, ES 0.35).

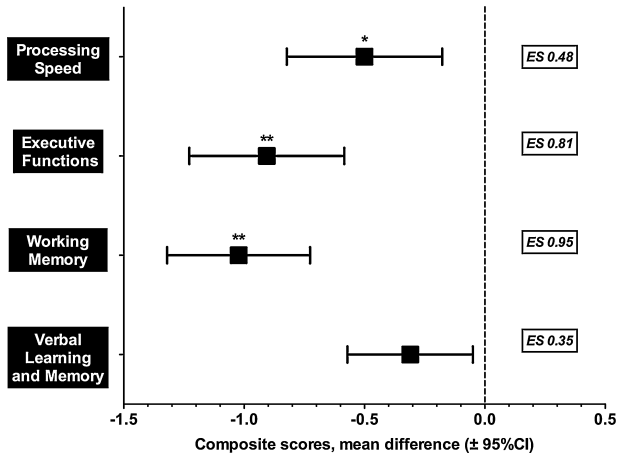

Fig. 1. Composite scores for the four tested neurocognitive domains in ALL survivors (N = 112) versus comparison peers. Linear regression, corrected for age, gender, and education. Mean difference in z-scores (±95%CI) shown. ES, effect size (Cohen's d). $^{*}P < 0.01$. $^{**}P < 0.001$.

Survivors: Poor Neurocognitive Performance Versus Good Neurocognitive Performance

The rate of poor performance (z-score less than −1.5) in survivors was 23% for processing speed, 31% for executive functions, 34% for working memory, and 16% for verbal learning and memory. Five survivors performed poorly in all four, five in three and 26 in two of the four tested cognitive domains. However, two-third of the survivors (68%) did not perform poorly in any (N = 46) or only one (N = 30) of the four domains.

TABLE II. Neuropsychological Test Results for Childhood ALL Survivors and Comparison Peers

	Survivors (N = 112)				Comparison peers (N = 100)					
Variables	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	Group difference (P value)[b]	Effect size (Cohen's d)
IQ[a]	113.9	10.0	87	135	112.0	9.5	90	139	0.22	0.19
Processing speed										
CWIT 1—color naming (sec)	29.8	5.3	18.0	45.0	27.3	4.1	19.0	38.0	0.001	0.52
CWIT 2—word reading (sec)	22.1	3.8	16.0	38.0	20.9	3.3	15.0	29.0	0.04	0.34
Executive functions										
CWIT 3—inhibition (sec)	54.6	13.1	32.0	100.0	46.0	8.8	29.0	67.0	<0.001	0.76
Interference effect (ratio)[c]	1.84	0.37	1.18	3.27	1.69	0.22	1.29	2.35	0.001	0.50
CWIT 4—inhibition/shifting (sec)	61.3	13.5	36.0	122.0	52.9	12.1	33.0	114.0	<0.001	0.65
Shift cost (ratio)[c]	2.08	0.43	1.25	3.76	1.95	0.42	1.19	3.93	0.03	0.30
Working memory										
Letter memory (max. 48)	39.2	4.4	25.0	47.0	42.4	3.7	28.0	48.0	<0.001	0.78
Keep track (max. 36)	22.7	4.5	4.0	31.0	26.4	3.9	16.0	33.0	<0.001	0.88
Verbal learning and memory										
CVLT-II—total recall (max. 80)	57.7	8.9	35.0	74.0	61.9	11.3	31.0	80.0	0.004[d]	0.42
CVLT-II—delayed recall (max. 16)	13.4	2.5	6.0	16.0	14.0	2.2	7.0	14.0	0.13	0.25

Comparison of raw scores by means of linear regression. CWIT, color–word interference test; CVLT II, California verbal learning test; Interference effect (CWIT), ratio completion times CWIT 3 (inhibition)/CWIT 1 (color naming); Shift cost (CWIT), ratio completion times CWIT 4 (inhibition/switching)/CWIT 1 (color naming); CWIT/interference effect/shift cost, lower value best; Letter memory/keep track/CVLT-II, higher value best.
[a]Estimated from Wechsler abbreviated scale of intelligence (WASI); [b]Adjusted for age (except IQ), sex, and years of education; [c]Not included in calculation of composite scores; [d]Did not remain significant when controlling for working memory ($P = 0.90$) or processing speed ($P = 0.03$).

Gender, age at diagnosis, or follow-up time was not associated with poor cognitive performance (Supplemental Table SIII). Neither did we find any association between increased cumulative doses of methotrexate and poor cognitive performance. We even observed a trend toward higher cumulative doses of IV MTX in survivors with normal working memory compared to those performing poorly ($P < 0.04$). The number of intrathecal methotrexate administrations and cumulative doses of IV methotrexate was almost identical for survivors with poor and normal performance. Furthermore, neither larger cumulative doses of steroids, cytarabine, vincristine, anthracyclines, nor treatment with dexamethasone versus prednisolone only or duration of maintenance treatment disclosed any associations with impaired neurocognitive outcome (Supplemental Table SIII).

Older age at investigation was associated with poorer working memory in survivors (OR 1.08, 95%CI 1.02–1.15, *P* 0.007), but not in comparison peers (OR 1.07, 95%CI 0.97–1.17, *P* 0.17). However, mean age between survivors and comparison peers with poor working memory did not differ significantly (31.0 ± 7.5 vs. 33.9 ± 9.7 years; OR 0.95, 95%CI 0.86–1.60, *P* 0.37).

DISCUSSION

The results of this long-term follow-up study indicate that 7–40 years after treatment with chemotherapy only, ALL survivors show significant deficits on a group level in processing speed, executive functions, and working memory compared to comparison peers, albeit similar general intellectual ability. We did not identify any treatment- or disease-related factors associated with poor cognitive functioning in survivors.

General intelligence measured by IQ did not differ between our ALL survivor sample and comparison peers. This is consistent with the findings of several other studies with shorter follow-up time,[8,9,27] supporting the hypothesis that general intellectual ability in ALL survivors is not affected by treatment with chemotherapy only. Although total IQ estimated by WASI correlates well with total IQ measured by a full-scale IQ test (WAIS-III),[28] the above-average IQ level in both survivors and comparison peers must be interpreted with caution, as scoring results are based on US WASI norms and may overestimate IQ in the Norwegian population, according to a recently published review.[29]

However, despite similar IQ, deficits in specific cognitive domains emerged in ALL survivors. It has been previously shown that such deficits may be unrelated to general intelligence.[30] The executive functions' tests address the target functions inhibition, meaning deliberately suppressing an automatic response, and shifting, meaning attention shifting back and forth between multiple tasks or mental sets.[16] Survivors performed more poorly in all subtests, but part of the impairment disappeared when controlling for processing speed. Thus, the survivors' poorer performance for executive functions could be contributed to difficulty in the inhibition condition rather than any added cost of shifting. Interestingly, we have recently reported self-rated executive impairment in only 16% in an almost identical survivor sample,[31] in contrast to 31% in the performance-based tests. Similar findings have been described previously and may be explained by long-term adaptation or lack of insight.[32] The most pronounced impairment was seen in the domain working memory, which involves monitoring and updating information held in the short-term memory. Concerning verbal learning and memory, the group difference between survivors and comparison peers was small and disappeared when controlling for working memory and, in part, processing speed. It seems that verbal memory itself in survivors is not impaired, whereas acquisition of new information takes longer time, mainly due to impaired working memory. Taken together, working memory/executive function and, to a lesser degree, processing speed, seem to be the key functions affected by CNS-directed chemotherapy. Similar results have been reported from studies with shorter follow-up time[5,6,10,11,33] and a recent long-term study from the St. Jude Cohort that did not include an untreated comparison group.[32] Difficulties in specific cognitive domains, albeit good general intellectual ability, may have a huge impact on education, work, and organizing everyday life. Our findings indicate that this pattern persists in survivors many years from diagnosis and well into adulthood.

We did not identify any association between higher individual cumulative doses of cytotoxic agents and long-term cognitive impairment. Also, we have recently shown a lack of association between treatment variables and neuroanatomical volumes in a partly overlapping survivor sample.[34] Previous studies on the relationship between cumulative MTX doses and cognitive functioning have shown conflicting results. One study reported greater attention deficits in children who received higher doses of IV MTX,[35] whereas other investigators failed to identify an association between IV or IT MTX doses and neurocognitive outcome,[7,36] in accordance to our findings. These contradicting results may in part be due to varying sample sizes, follow-up times, and the inclusion of radiotherapy-treated survivors in some studies. Corticosteroids, especially dexamethasone, have been associated with reduced memory, but findings in ALL survivors have been inconsistent.[37,38] Cytarabine can cause acute neurotoxicity,[39] but to our knowledge, the effect on cognitive functioning has not been addressed before. Again, we observed no relationship between cumulative doses and long-term cognitive outcome.

Due to the long observation time, factors other than cumulative treatment load may have had a strong impact on cognitive long-term outcome in our ALL survivors. Interestingly, almost half of the survivors in our study were not impaired in any of the cognitive domains tested, whereas others showed severe deficits in several domains. A number of theories on mechanisms of the neurotoxicity in cancer and its treatment have been proposed,[40] and the effect of secondary inflammatory responses and vascular injury may be unrelated to treatment intensity. Genetic factors may contribute to individual vulnerability to CNS-directed chemotherapy. A recent study observed an association between folate pathway polymorphisms and attention and processing speed deficits, whereas cumulative MTX doses, gender, or age at diagnosis were unrelated to cognitive outcome.[41] On the other hand, protective factors, such as cognitive reserve and a healthy lifestyle, may play an important role in preserving cognitive functioning.[39]

Working memory is one of the first cognitive functions to decline with age,[42] and chemotherapy has been associated with early aging in various organs, including the brain.[40,43] In our study, older survivors were more likely to show poor working memory, whereas we did not see this effect in comparison peers, but the group difference was not significant. Similarly, Schuitema et al. [44] only found a mild effect of chemotherapy compared to radiotherapy on age-associated neuropsychological dysfunction in long-term survivors of pediatric lymphoid malignancies. However,

longitudinal studies are needed to map how cognitive functions in ALL survivors change with age.

This study is limited by its cross-sectional design that did not allow longitudinal neuropsychological assessment or comparison to baseline data. The long follow-up time allows for confounders not related to leukemia and its treatment. Survivors had lower educational attainment than comparison peers, and even though we adjusted for this in the analyses, this also could be a consequence of the survivors' cognitive impairment. Due to the long follow-up time, it was not possible to adjust for baseline socioeconomic status. However, social differences in Norway are small compared to, for example, the US, and equal health and educational services are available to all inhabitants. Finally, the survivors were treated with different multi-agent protocols, which may make interpretation of the data more difficult. However, we calculated actually delivered cumulative doses for each survivor as recommended by Oeffinger, [45] thereby taking into account individual dose reductions or changes in treatment plans. The major strengths of our study are the long follow-up time and the representative sample of survivors, having invited one-half of the eligible Norwegian ALL survivors with few patients lost to follow-up and an acceptable response rate.

In conclusion, long-term survivors of childhood ALL treated exclusively with chemotherapy showed no impairment in intellectual ability, but significantly poorer performance in processing speed, executive functions, and working memory than comparison peers. We did not identify any association with higher treatment burden, age at diagnosis, or gender.

As follow-up time for ALL survivors treated exclusively with chemotherapy has been limited until now, there is a need for future long-term studies to investigate development in cognitive function over time and to identify both survivors at risk for cognitive late effects and protective factors. It is, however, equally important to develop strategies to help survivors with deficits in the domains at risk.

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