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Intellectual development of childhood ALL patients: a multicenter longitudinal study

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Abstract

***Background*: In childhood acute lymphoblastic leukemia (ALL), radiotherapy for CNS prophylaxis is not used in frontline therapy anymore. Standard treatment for ALL nowadays consists of polychemotherapy. Therefore, assessment of potential chemotherapy-induced cognitive side effects becomes important. Although neurotoxicity was demonstrated in cross-sectional studies, longitudinal studies remain scarce.**

***Procedure*: We evaluated intellectual development of 94 pediatric ALL patients between 1990 and 1997, diagnosed before the age of 12 years, treated according to the European Organisation for Research and Treatment of Cancer Children's Leukemia Group 58881 protocol. Three assessments of the Wechsler Intelligence Scale for Children Revised were performed since diagnosis, according to age. Using repeated measures regression analysis, we investigated the effect of gender (low versus increased) risk group, parents' education, age at diagnosis, intelligence quotient (IQ) subscale (verbal (VIQ) versus performance (PIQ) intelligence), and test session.**

***Results*: PIQ scores were lower than VIQ at baseline (−5.3 points on average, $p = 0.0032$), yet PIQ increased more strongly (PIQ: +3.9 points per test session; VIQ: +0.8, $p = 0.0079$), so this baseline difference disappeared ($p = 0.0079$). There were no clear effects of gender (girls: +0.6 points; $p = 0.78$) or risk group (low risk: +1.5 points; $p = 0.49$), but IQ scores were higher when one parent had followed higher education (+9.5 points, $p < 0.0001$). Finally, diagnosis at younger age predicted lower IQ scores (−1.3 points per year, $p = 0.0009$).**

***Conclusion*: Given that IQ scores did not decline, our findings demonstrate a stable pattern. However, the lower PIQ scores at baseline may indicate that performance functioning is vulnerable to acute neurotoxicity. Also, lower scores for younger patients highlight the stronger impact of the disease and/or treatment at younger age.**

Introduction

Remaining physical [1] and psychological symptoms [2] often affect daily life of pediatric cancer survivors to a large extent. Because survival rates of pediatric cancer patients continue to increase, factors that influence their quality of life receive more and more attention. During childhood, one important factor that influences daily life is performance at school [3]. School results often decline once a child is diagnosed with cancer [4]. The disease as well as the treatment can have an important impact on cognitive development. On the one hand, it is possible that cancer and/or chemotherapy induce physiological neurotoxic mechanisms. On the other hand, because of intensive treatment, also functioning at school can be delayed. For pediatric cancer patients it was shown that cognitive deficits thoroughly limit their overall functioning in daily life [5]. Brown and colleagues for instance demonstrated that children treated for acute lymphoblastic leukemia (ALL) obtained lower scores on intelligence tests than control participants [6].

During the last few years, evidence for potential treatment-induced neurotoxicity in pediatric oncology is increasing. So far, most evidence exists for brain tumor and ALL patients [7–9]. However, these neurotoxic effects are mostly induced by radiotherapy (RT) [10–12]. Also, in ALL patients, neurocognitive functioning was mostly affected in case of chemotherapy in combination with RT [13–15]. To limit RT-induced neurotoxic adverse effects, therapies changed throughout time towards chemotherapy-only treatments. Given that ALL nowadays is generally treated with chemotherapy only and prophylactic central nervous system (CNS)-

directed RT is abandoned, the long-term effects of chemotherapy become more important to address [16,17]. Chemotherapy for ALL includes CNS-directed prophylaxis, that is, intrathecal (IT) chemotherapy, as well as high-dose intravenous methotrexate (HD-MTX). HD-MTX can, however, cause serious acute neurological symptoms in patients [18]. Also, animal studies evidenced neurotoxic effects, affecting both behavior as well as neurophysiology [19–22]. For chemotherapy only, magnetic resonance imaging studies indicated smaller grey matter volumes [23,24] as well as decline in white matter integrity [13,15] and white matter hyperintensities [25] in ALL survivors compared with controls.

So far, survivor studies including neuropsychological assessments of chemotherapy-only treated patients showed impairment of several neurocognitive functions. These include memory [26], specific attentional skills [27], visuomotor control [28], and verbal and nonverbal functioning [29].

However, evidence for such specific deficits remain inconsistent [30,31]. Furthermore, general intelligence quotient (IQ) scores of ALL patients also remain within the normal range [16].

All of the previously mentioned studies used a cross-sectional design. Although they showed neurocognitive sequelae, it remains unclear how cognitive functioning of the children evolves throughout their development. Given that this has important consequences for education and academic functioning of these patients later in life, longitudinal designs are essential to acquire a better understanding of cognitive and intellectual development over time in children treated for ALL. Only a few longitudinal studies were performed. Brown and colleagues (1999) concluded a decrement in intellectual functioning in children receiving CNS-prophylactic chemotherapy for leukemia [6]. In a small series of 16 CNS-directed treated patients (including acute lymphoblastic leukemia, acute myeloid leukemia, and T-cell lymphoma) and 10 non-CNS treated patients, they yearly acquired IQ scores from diagnosis on, during 5 years. Later, Kingma and colleagues (2002) investigated a broader range of functions, by assessing IQ scores as well as memory and attentional functioning [32]. Unpaired *t*-tests resulted in a significantly lower VIQ and executive performance for patients, but only 5 years after diagnosis. Recently, Halsey and colleagues (2011) demonstrated significantly lower IQ scores for ALL patients throughout development compared with controls, independently from MTX dose [33]. These researchers used intervals of 0.5, 3, and 5 years after diagnosis. Jansen and colleagues did not encounter such differences between patients and siblings, not at baseline, nor after treatment [34]. All of these longitudinal studies used different IQ measurements during their study, and variable assessment schedules according to the patient's age. In our study, we used one consistent intelligence test for a large population. Intelligence scores were assessed three times with an average interval of 3 years.

Methods

Patients

This is a cohort study of 94 Belgian Dutch-speaking childhood ALL patients between the age of 2 and 12 years at diagnosis, who were newly diagnosed with ALL between 1990 and 1997 at the University Hospitals of Ghent and Leuven in Belgium. Out of 144 childhood leukemia patients, 50 patients were excluded because of predefined exclusion criteria: exceeding the age range ($n = 17$, <2 years old or >12 years old at diagnosis), other diagnosis ($n = 25$, high-risk ALL, CNS involvement, mature B-cell ALL, or relapse), early death ($n = 1$), missing data ($n = 5$), and refusal of the parent ($n = 2$). Data were only complete if all subscales of the IQ test were acquired. The median age at diagnosis was 4.4 years (range 2.0–11.9 years). The majority of the patients was younger than 6 years old at diagnosis ($n = 60$). All of the patients were treated according to the European Organisation for Research and Treatment of Cancer Children's Leukemia Group 58881 trial [35,36], a Berlin–Frankfurt–Munster-based protocol, which consisted of CNS prophylaxis with intrathecal methotrexate (IT-MTX) and HD-MTX (5 g/m^2). No one received cranial RT. Only patients from the low ($n = 53$) and increased (n = 41) risk groups were included, whereas high-risk patients (i.e., corticoresistent after prophase therapy; did not achieve complete remission after induction therapy; undifferentiated immunophenotype with absence of B cell, T cell, myeloid markers, or common acute lymphoblastic leukemia antigen; and certain cytogenetic characteristics: *t*(9;22), *t*(4;11), or near-haploidy) were excluded, given their elevated chance of relapse during the first year of therapy [35,36].

Design

We used the Dutch-translated version of the Wechsler Intelligence Scale for Children Revised (WISC-R). Given that we attempted to test with consistent materials throughout the study, and the WISC-R test can only be performed between 6 and 17 years old, first assessments were only established once patients had reached the age of 6 years old. A schematic overview of our design is presented in Figure 1a. Cognitive functioning was evaluated at three time points, according to their age. Given the age range limitations of the test, only patients younger than 12 years at diagnosis were included. We excluded patients younger than 2 years old to avoid too large intervals between diagnosis and the first neuropsychological assessment.

All patients between 2 and 6 years old at diagnosis were tested at baseline (T1), as soon as they reached the minimal age (i.e., 6 years) for testing. For all other ages,

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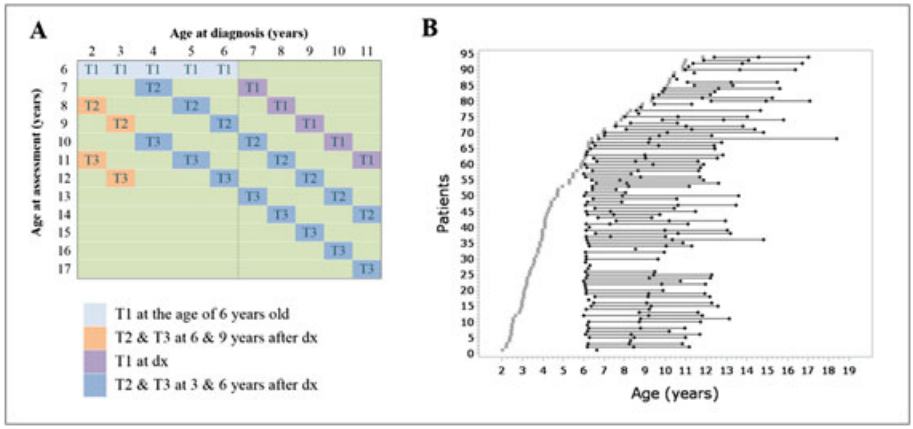

Figure 1. Design for assessments. (a) The longitudinal design of the study: three neuropsychological assessments over time (T1), (T2), and (T3), for each age at diagnosis (dx). Patients who were diagnosed younger than 6 years old were tested once they reached the age of 6 years. Two-year-old and three-year-old patients were tested a second and third time 6 years after diagnosis and 9 years after diagnosis, respectively. Patients between 4 and 6 years old were tested a second and third time 3 and 6 years after diagnosis, respectively. Patients older than 6 years old were tested within the first year after diagnosis, 3 and 6 years after diagnosis. (b) The schedule of assessments (for each patient separately): age at diagnosis (x) is plotted against each test session (dots). Patients are sorted by age at diagnosis

baseline testing was executed at diagnosis if the patients were in a good clinical condition. Assessments were acquired within 12 months after diagnosis, avoiding periods when steroids were administered. Two-year-old and three-year-old patients at diagnosis had their second and third assessments 6 and 9 years after diagnosis, respectively. All other patients' second and third neuropsychological assessments were planned 3 (T2) and 6 (T3) years after diagnosis. As a consequence, the interval between diagnosis and T2 was larger than 3 years (maximum of 6 years) for the two-year-old and three-year-old patients. For a detailed time schedule for all subjects, see Figure 1b.

Socio-economic status (SES) was defined by the educational level of the parents. We defined educational level as a binary variable. Education was considered as 'high' if one parent had obtained a degree of higher education after high school.

Statistical analysis

Socio-demographic predictors such as SES) [37] and gender [38] can affect intellectual outcome in children. We selected the following predictors a priori for the multivariate model to predict IQ scores: gender, risk group, education of the parents, age at diagnosis, IQ scale (verbal versus performance), and test session (first, second, and third). The last two variables are repeated measures (within-subjects variables). First, we evaluated the correlations between these predictor variables to address their possible interdependence before setting up our model.

Second, given the different approach for children diagnosed before versus after the age of 6 (see the *Design* section), we investigated whether age at diagnosis had a different effect on IQ for the patients who were diagnosed before the age of 6 than for patients who were diagnosed after the age of 6 (i.e., a 'piecewise effect' for age at diagnosis). This was performed to account for the fact that children before 6 years old had already received or even completed chemotherapy, whereas for older children, the first measurement was at diagnosis.

Third, we decided a priori to only assess interaction effects of test session with gender, IQ scale, and age at diagnosis. One joint likelihood ratio test was used to test for statistical significance at the 5% alpha level when adding all three interaction terms. If significant, the strongest interaction term was added, and a second joint test was performed for the remaining two. We used fixed effects repeated measures regression with PROC MIXED in SAS v9.4 (SAS Institute, Cary, NC, USA). The first-order autoregressive covariance structure was used to model the longitudinal effect of test session.

Results

Descriptive statistics

Descriptive statistics of predictors and outcomes are presented in Table 1. From the 94 patients, the study was discontinued for 38 patients (40%), of which 11 (29%) was because of death, 24 (63%) because of refusal for further participation, and 3 (8%) because of relapse or second malignancy. The median verbal IQ was 105 (interquartile range (IQR): 96–115) at the first testing and 108 (IQR: 97–119) at the third testing. The median performance IQ was 99 at the first testing (IQR: 88–111) and 109 at the third testing (IQR: 99–122).

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Table 1. Patient characteristics and descriptive data

	N	Percentage
	n	Median (IQR[1])	Range
Girls versus boys		46 versus 48	49% versus 51%
Low versus increased risk		53 versus 41	56% versus 44%
Higher versus lower education of parents		45 versus 49	48% versus 52%
Age at diagnosis (years)	94	4.4 (3.2–7.0)	2.0–11.9
Age at testing (years)			
Testing 1	94	6.4 (6.1–8.3)	6.0–12.4
Testing 2	70	9.5 (8.7–10.6)	7.3–14.9
Testing 3	56	12.3 (11.6–13.9)	9.7–18.4
VIQ			
Testing 1	94	105 (96–115)	79–145
Testing 2	70	106 (95–120)	76–150
Testing 3	56	108 (97–119)	76–143
PIQ			
Testing 1	94	99 (88–111)	71–150
Testing 2	70	104 (97–116)	76–137
Testing 3	56	109 (99–122)	74–137
TIQ			
Testing 1	94	102 (94–115)	79–142
Testing 2	70	108 (96–121)	78–141
Testing 3	56	108 (100–122)	78–139

[1]Interqartile range (IQR) = middle 50% of the data.

Selection of predictors in repeated measures mixed effect regression model

We checked whether the effect of age at diagnosis was different before and after 6 years, given the different approach for children diagnosed before and after the age of 6. There was little evidence of such a 'piecewise' effect for age at diagnosis ($p = 0.44$).

Regarding the selection of interaction terms, the joint likelihood ratio test for the three a priori selected interaction terms was statistically significant ($p = 0.007$), resulting in the inclusion of the interaction between IQ scale and test session into the final regression model. The joint test for the remaining two interaction terms was not statistically significant ($p = 0.25$), such that these latter interactions were not considered further.

Repeated measures regression analysis

Concerning the demographic factors, IQ scores had a weak relationship with gender (girls: +0.6 points on average; $p = 0.78$) and with risk group (low risk: +1.5 points; $p = 0.49$) (Table 2). Parental education by contrast was related to differences in intelligence scores. More specifically, children of whom at least one parent finished higher education obtain an IQ score that is on average 9.5 points higher ($p < 0.0001$).

Furthermore, patients who were diagnosed at a younger age obtained lower IQ scores at baseline, with an average decrease of 1.3 points per year ($p = 0.0009$). Notably, a different pattern was observed for the two IQ subscales (i.e., performance IQ versus verbal IQ). More specifically, at baseline assessment VIQ was higher than PIQ (+5.3 points; $p = 0.0032$). In addition, there was an interaction effect between IQ subscale and test session ($p = 0.0079$): whereas VIQ scores increased only to a limited extent (+0.8 points per session; $p = 0.39$) (Figure 2a) and PIQ scores increased more strongly (+3.9 points per session) (Figure 2b). As a result, the difference between PIQ and VIQ at baseline disappeared over time (Figure 2c) (predicted IQ scores for each subscale for a patient diagnosed at 4 years old are illustrated in Figure S1 in the Supporting Information). (Detailed descriptive data of the subscale scores at each assessment are reported in Table S1 in the Supporting Information.)

Table 2. Results of mixed model regression analysis predicting IQ scores

Predictor	Coefficient	SE	95% CI	*p*
Intercept	*103.0*	*3.55*		
Boy versus girl	−0.6	2.16	−4.9 to 3.7	0.78
Low versus increased risk	1.5	2.16	−2.8 to 5.7	0.49
Lower versus higher education	−9.5	2.19	−13.9 to −5.2	<0.0001*
Age at diagnosis (per year)	1.3	0.40	0.6 to 2.1	0.0009*
PIQ versus VIQ[2]	−5.3	1.78	−8.9 to −1.8	0.0032*
Test session (0, 1, and 2)[2]	0.8	0.94	−1.1 to 2.7	0.39
Test session by IQ scale interaction[1]	3.1	1.14	0.8 to 5.3	0.0079*

[1]This refers to interaction effects with age at testing.
[2]Because of the interaction effects with age at testing, these effects represent the effect at the reference level (i.e., the main effect of IQ scale represents the difference between PIQ and VIQ at first test session; the main effect of test session represents the increase in average IQ score for VIQ. The interaction term coefficient represents the increase in average IQ score per test session for PIQ).
*Indicates *p*-values < 0.01.

Discussion

In this longitudinal study, we investigated the potential neurotoxic effects of chemotherapy-only treatment in ALL patients without CNS involvement. For these patients, we did not encounter decrements (or lack of increase) in IQ scores. After controlling for the effect of parental education as indicator of SES, we observed that VIQ scores increased only limitedly for ALL patients throughout and after treatment. However, we found that PIQ scores were lower than VIQ at baseline and increased more strongly. Furthermore, we encountered lower IQ scores for patients who were diagnosed at younger age. Seeing the different approach for children diagnosed before versus after the age of 6 (see the *Design* section), the youngest patients already finished their therapy before their first assessment. Given that the most intensive phase of IT-MTX and intravenous HD-MTX is scheduled during the first 6 months of treatment, lower PIQ scores at baseline may indicate a stronger acute vulnerability to chemotherapy of performance functioning, with the youngest patients being the most vulnerable. The lower PIQ scores at baseline and stronger impact for younger patients can both be because of the chemotherapy as well as to the

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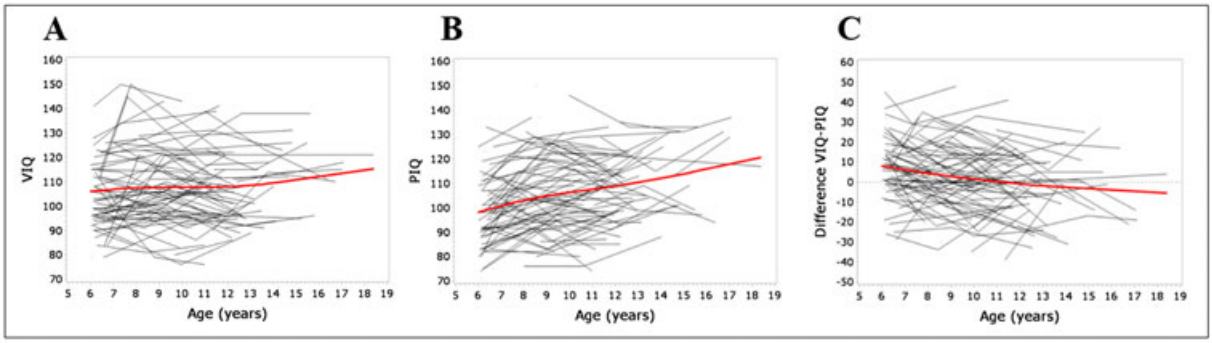

Figure 2. Spaghetti plots. The red line shows the average relationship between IQ and age (obtained with spline smoothing). (a) Spaghetti plot of VIQ scores. (b) Spaghetti plot of the PIQ scores. (c) Spaghetti plot of the difference between VIQ and PIQ (positive result means verbal IQ was higher than performance IQ)

disease itself. To further explore this hypothesis, performance functioning was plotted against duration between first assessment and diagnosis (Figure S2). A decrease is observed during the first 2 years, which demonstrates an acute decline. By contrast, patients who were tested at least 2.5 years after diagnosis at first assessment show higher PIQ scores at first assessment. This could again suggest a recovery pattern. Still, notice that treatment protocols between both risk groups did not differ to a large extent (Table S2). Given that tumor burden reflected by low versus increased risk did not result in different IQ scores, and CNS positive patients were excluded, we suggest that such an acute neurotoxic effect should be assigned to the treatment rather than to the disease burden. Importantly, most ALL patients are diagnosed between 3 and 5 years old. Yet, for these ages, IQ testing is less reliable. Therefore, although patients differed in their treatment progress, this design permitted us to use the same test materials (WISC-R) and consistent norms for all patients. Despite a dropout of 40% after the second measurement, we could still acquire intelligence scores for a second time for 70 patients, of which 56 patients participated a third time. We mention that for the dropout group ($n = 38$), the majority of the patients had lower education of the parent (60.53%). Given that education of the parents was a significant predictor in our analysis, this specific dropout might have resulted in a stronger positive trend of the remaining data.

Considering the earlier neuropsychological longitudinal studies, other studies did show decrements in IQ scores [6,32,33]. However, notice that in these earlier studies, IQ materials changed for some patients throughout time, and analyses did not include covariates. By contrast, Jansen et al. [34] also showed rather stable IQ scores of chemotherapy-only treated ALL patients. Still, they also demonstrated that PIQ was lower for younger patients (at diagnosis). Our finding of lower PIQ at baseline suggests an acute decline in performance cognitive functioning for ALL patients, whereas verbal functions are preserved. Consistent with the results of Jansen and colleagues, the most strongly affected patients in our study appeared to be the younger patients at diagnosis. Other studies with regard to brain vulnerability during development also evidenced stronger vulnerability in younger children, such as early pediatric head injury [40] and RT in ALL patients [18]. Although Halsey and colleagues [33] did not find differences between IT-MTX + HD-MTX versus IT-MTX only, they did encounter lower IQ scores for patients than control participants at second (i.e., 3 years after diagnosis) and third (i.e., 5 years after diagnosis) assessments. More specifically, scores of control participants increased throughout development, whereas these patient groups (treated with either HD-MTX, IT-MTX or RT) remained stable. The increase in these scores for control participants could partly be explained by the Flynn effect (i.e., the observed rise in norm IQ scores over time, with an estimated increase of 3 IQ points per decade [39]). As a result, norms become obsolete. Therefore, the stability of patients' scores could indicate an inhibition of such growth in intelligence. Comparably, in our study, the increase in IQ scores that we observed in patients could also have been stronger if no chemotherapy was administered. Given that we did not have data available about premorbid intellectual functioning, nor from control groups, it remains difficult to estimate the impact of the Flynn effect on these results. Unfortunately, premorbid screening for IQ and exact timing of control assessments remain challenging to acquire in time.

With regard to the increase of IQ scores throughout development, we encountered the strongest increase in performance functioning with time (i.e., 'measurement') in comparison to verbal functioning. This suggests that for the lower PIQ scores at first assessment, compensation arises throughout development (Figure S2). In this context, Anderson and colleagues discussed plasticity of the younger brain [40]. In their review, they report the potential regeneration of new neurons as well as new

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connections (i.e., so-called sprouting). The stronger increase in PIQ scores might be because of stronger practice or rehabilitation effects for PIQ than for VIQ, as Halsey and colleagues earlier suggested [33]. However, in our study, we did not register whether patients attended specialized rehabilitation programs (e.g., with physiotherapists, speech therapists, and teachers) or special care. If this information could be accounted for in the future, the distinction between rehabilitation effects will become much clearer.

Finally, it is important to mention that we used general IQ measurements. Besides our longitudinal study and the study of Jansen and colleagues [34], also, cross-sectional studies generally show average IQ scores for ALL patients compared with norm scores. By consistently using more specific measurements of attention, memory, and executive functioning, as well as control groups, chemotherapy-induced sequelae could be investigated more in detail.

Conclusion

In contrast to the existing evidence for long-term neurotoxicity because of RT, we showed that IQ scores of chemotherapy-only treated ALL patients increase only a little for VIQ, but increase more strongly for PIQ. Still, lower IQ scores for patients who were diagnosed at younger ages highlight the stronger impact of the disease and/or treatment at younger age. Given that the tumor burden reflected by low versus increased risk did not meaningfully affect IQ scores, we would assign this effect to treatment rather than to the disease burden. Although comparable to the normative range, PIQ was lower than VIQ at baseline. Given that patients already started therapy at first assessment, this could indicate that performance functioning is most vulnerable to acute neurotoxicity at baseline, specifically for patients diagnosed at younger age. Nevertheless, patients appear to catch up with a stronger increase in PIQ scores, which possibly indicates that PIQ is being trained more easily than VIQ. Still, given earlier evidence for delay in development of specific cognitive functions from cross-sectional studies, new longitudinal studies measuring more specific cognitive functioning will be required to address this question in the future. Also, to investigate the impact of disease versus treatment on cognition, it is recommended to implement neuro-imaging and behavioral assessments at baseline before treatment starts.

Conflict of interest

The authors have declared no conflicts of interest.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site.

Figure S1. Illustration of predicted IQ scores for each subscale PIQ and VIQ. This is an illustration of the observed interaction between IQ scale (verbal versus performance) and test session. The lines show the predicted IQ for a patient diagnosed at 4 years based on the repeated measures regression model. The predictions are averaged over gender, risk, and education of parents.

Figure S2. Interval between diagnosis and first assessment is plotted against PIQ scores. The red line indicates an (spline smoothed) evolution pattern in PIQ scores (for all patients, of all ages). The blue dotted line indicates the visually estimated point of recovery after the potential acute neurotoxicity.

Table S1. Mean scores (with standard deviations) for each subscale.

Table S2. EORTC CLG 58881: treatment protocol for low versus increased risk patients.